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Impact of an Exercise Program on Stress, Fatigue, and Quality of Life for Individuals Living with Primary Immunodeficiency Disease

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The Impact of an Exercise Program on Stress, Fatigue, and Quality of Life for Individuals Living with Primary Immunodeficiency Disease

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Approval/Signature Page

We hereby certify that this dissertation, submitted by Kerri L. Sowers, conforms to acceptable standards and is fully adequate in scope and quality to fulfill the dissertation requirement for the degree of Doctor of Philosophy in Physical Therapy.

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Abstract

Background: There are over 300 Primary Immunodeficiency diseases (PID) that are a result of a genetic or idiopathic dysfunction of any aspect of the immune system. These conditions result in a higher frequency of infections, autoimmune conditions, or malignancies. Moderate intensity exercise is thought to help the immune system, while high intensity exercise may have a negative impact on immune function. The impact of exercise on individuals with an impaired immune system due to PID is not yet understood. ***Purpose***: The purpose of this study was to investigate whether a low to moderate intensity exercise program would have an effect on stress, fatigue, and quality of life (QoL) for individuals diagnosed with PID. ***Methods***: 34 participants were included in this eight-week, mixed-methods, randomized controlled trial, either as part of the control group, or as part of the exercise intervention group. Participants completed pre- and post-study outcome measures, reflective journaling, and a post-study interview. ***Results***: There were no statistically significant differences between the groups for the outcome measures, infection incidence, or need for non-routine medical care. There was a clinically significant decline in the Physical Component Summary score of the SF-36v2 for the control group at the end of the study. The scores for the SF-36v2, for all participants, were below normative scores for all domains, at the beginning and end of the study. Four main themes emerged from the qualitative interviews: living with a 'new normal', the challenges of living with a chronic disease, facing the stigma of a chronic disease, and wanting to exercise, but were too exhausted to do so. ***Conclusions***: Individuals with a diagnosis of PID have lower QoL scores as compared to population norms. They face high levels of stress, overwhelming fatigue, social isolation, and decreased emotional well-being. Exercise programs for this patient population did not result in increased infections or need for non-routine medical care but did result in emotional implications

that need to be considered. Healthcare providers need to address emotional well-being and provide coping strategies. Exercise programs should be designed with a slow, methodical ramp-up to avoid increasing fatigue or stress, while exercise goals must be highly achievable and realistic. Physical therapists should collaborate with other healthcare professionals for a more holistic and interprofessional approach to working with patients with a diagnosis of PID.

Keywords: primary immunodeficiency disease, exercise, stress, fatigue, quality of life, emotional well-being, health-related quality of life, identity

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"No one can whistle a symphony. It takes a whole orchestra to play it."

– H.E. Luccock

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Introduction to the Chapter

Primary immunodeficiency diseases (PID) are rare, heterogeneous, genetic disorders that are characterized by an increase in recurrent infections, autoimmunity, inflammatory responses, and malignancy. Individuals with a diagnosis of PID had a poorer health-related quality of life (HRQoL) compared to healthy individuals, primarily in the areas of physical function, self-esteem, and family activities (Dinakar, 2006). It is important to identify cost-effective and safe treatments that will help to reduce stress and fatigue, and improve quality of life (QoL), in patients with a chronic illness, such as PID. There are currently no published studies investigating the use of an exercise intervention with the PID patient population.

Problem Statement and Goal

PIDs are a group of rare genetic disorders in which immune system function is impaired. The International Union of Immunological Societies (IUIS) updated their classifications of PID in 2015. The IUIS added 34 new gene defects to their 2013 report, resulting in the identification of nearly 300 PID variations (Picard et al., 2015). This group of heterogenous disorders often results in an increased rate and severity of infection, autoimmune diseases, abnormal inflammatory responses, and malignancy (Berger, Murphy, Riley, Bergman, and The VIRTUE Trial Investigators, 2010; Bonilla et al., 2015; Picard et al., 2015). There are significant variations in the reported prevalence of PID, both in the United States and worldwide. While there are limited numbers of participants registered in PID data tracking programs, Bousfiha et al. (2013) estimated 270,193 individuals with PID in the United States.

Research conducted by Cunningham-Rundles, in 2012, indicates that individuals with a diagnosis of Common Variable Immune Deficiency (CVID), one of the more prevalent variants of PID, suffer from acute and chronic infections, inflammatory and autoimmune diseases, and elevated incidence of cancer and lymphoma. Quinti et al. (2012) and Tabolli et al. (2014) both showed low values of HRQoL relating to physical domains in patients with CVID.

The American Physical Therapy Association (APTA) recognizes that physical therapists are experts in exercise, and that regular physical activity can be used to improve wellness and QoL, especially in individuals with chronic illness (APTA, 2012). Individuals who participate in physical activity reported improved QoL and physical health; even low intensity activity is linked to improved health outcomes in chronic diseases (Apostolopoulos, Borkoles, Polman and Stojanovska, 2014). Physical therapists are integral in helping to identify the benefits and safety of exercise, and in guiding a structured exercise program for patients who are affected by a chronic disease.

This research study investigated the effect of low to moderate intensity exercise program on stress, fatigue, and QoL in individuals diagnosed with PID. This research also aimed to better understand the experiences of patients diagnosed with PID, and their experiences while they participated in an exercise program. This was accomplished with the use of a mixed methods approach, which incorporated both quantitative and qualitative measures. A guided exercise program, with repeated assessment of standardized outcome measures and tracking of infection incidence for participants who had diagnosis of PID, comprised the quantitative portion of this study. Interpretive phenomenology was used to understand the experiences of the participants, through interviews and journaling.

Relevance and Significance

The APTA supports the role of physical therapists as exercise experts for chronic health issues and improved wellness (APTA, 2012). Patients diagnosed with PID are often plagued by chronic medical conditions and the related issues of stress, fatigue and decreased QoL. A study by Tcheurekdjian, Palermo, and Hostoffer (2004) found that patients with CVID have a significantly worse HRQoL as compared to other patients with chronic illness (such as diabetes mellitus or congestive heart failure). Investigations into QoL for patients with PID showed an increased risk for anxiety and depression, due to the chronic nature of the disease and its associated complications (Quinti et al., 2012; Tabolli et al, 2014).

It is important to identify cost-effective and safe treatments that will help to improve QoL, and reduce stress and fatigue, in patients with a chronic illness. Pre-diagnosis costs for a patient with a PID was estimated to be US $138,760, annually, while post-diagnosis costs dropped to US $60,297, annually (Modell et al., 2011). A recent publication by Sadeghi, Abolhassani, Naseri, Rezaei and Aghamohammadi (2015) found the total estimated cost of diagnosed CVID to be US $274,200, per patient, annually; the largest percentage of the cost was to provide monthly immunoglobulin replacement.

Research has noted that regular exercise is linked to improved physical and mental health outcomes for a multitude of chronic medical conditions (Apostolopoulos et al., 2014). Based on these findings, it is reasonable to expect that exercise can provide the same type of benefits to patients with a diagnosis of PID. Exercise was also found to have anti-inflammatory effects, which may be beneficial in chronic diseases (Gleeson et al., 2011a). In some chronic diseases, exercise (as a therapeutic intervention) was found to be as effective as medication, due to its anti-inflammatory and immunomodulatory effects (Lancaster and Febbraio, 2014).

While there exists a possibility for improvement in HRQoL due to exercise participation, it is also critical to determine the safety profile of exercise in this specific population. Due to its potential impairment in immunity, prolonged or vigorous activity may put this patient population at risk for increased infection incidence. In contrast, moderate intensity exercise boosted immunity in other patient populations (Simpson & Bosch, 2014), and may prove beneficial to patients with a diagnosis of PID. As PID is a chronic disease, with significant reductions in HRQoL, it is important to identify the potential impact of exercise on this population.

The PID patient population is small, and exact numbers are challenging to estimate due to the prolonged time from the onset of symptoms to diagnosis, currently estimated to be nine years (Boyle and Buckley, 2007). There are conflicting estimates relating to the prevalence of PID, primarily due to the disease often going undiagnosed for years. Research studies have provided a range from one to ten per 100,000 person-years, with a 2009 study by Joshi, Iyer, Hagan, St. Stauver, and Boyce suggesting an overall incidence of 4.6 per 100,000 person-years for the period of 1976 to 2006. While a physical therapist may not see patients diagnosed with PID as often as other chronic conditions, these patients may present for other medical impairments or for generalized impairments related to their PID. In addition, based on the APTA's stance defining physical therapists as exercise experts and promoters of health and wellness, it is important for physical therapists to understand the benefits of exercise for all chronic disease patient populations.

While a patient diagnosed with PID is often labeled immune-deficient, it is more appropriate to consider them as having an immune dysfunction. With that consideration, this research may permit generalizations to be made to patients with related autoimmune conditions. Perandini et al. (2012) has summarized multiple studies which show that aerobic and strength

training interventions will improve physical function and HRQoL, while reducing pain, without causing adverse events in various autoimmune conditions. While medically different, PID is a chronic disease and it shares several of the same impairments, and secondary complications, as many common chronic diseases.

Research Questions and Hypotheses

This research study sought to answer several important questions. The primary investigation was to determine whether a low to moderate intensity exercise program had an effect on stress, fatigue, and QoL, in participants with a diagnosis of PID. This research also sought to understand the lived experience of an individual diagnosed with PID, and their experience while they participated in a low to moderate level exercise program. This research also sought to provide evidence regarding the potential for adverse events associated with an exercise program for individuals with an immune-compromised diagnosis, as it related to infection incidence or need for non-routine medical intervention.

Quantitative Research Question One: Does a low to moderate intensity exercise program have an effect on stress, fatigue, and QoL, in participants with a diagnosis of PID?

> *Hypothesis (H_1):* Participants with a diagnosis of a PID will demonstrate a change in stress, fatigue, and QoL after participating in a low to moderate intensity exercise program.
>
> *Null Hypothesis (H_0):* Participants with a diagnosis of a PID will show no change in stress, fatigue, or QoL after participation in a low to moderate intensity exercise program.

Quantitative Research Question Two: This study will determine if a low to moderate intensity exercise program impacts the number of infections or non-routine medical visits in participants with a diagnosis of PID.

Hypothesis (H_1): Participants with a diagnosis of PID will demonstrate a change in the number of infections and non-routine medical visits after participating in a low to moderate level exercise program.

Null Hypothesis (H_0): Participants with a diagnosis of PID will demonstrate no change in the number of infections, and non-routine medical visits, after participating in a low to moderate level exercise program.

Qualitative Research Question: What is the lived experience of participants diagnosed with PID as it relates to stress, fatigue, QoL, and exercise?

Definition of Terms

Primary Immunodeficiency Disease (PID): a group of rare, chronic disorders where part of the immune system is missing or does not function properly.

Common Variable Immunodeficiency Disease (CVID): one of the most frequently diagnosed variants of PID, it is characterized by low levels of serum immunoglobulins and a decreased antibody response.

Severe Combined Immunodeficiency Disease (SCID): a potentially fatal PID where there is an absence of both T-lymphocyte and B-lymphocyte function.

Selective IgA Deficiency: a PID characterized by the absence of IgA, with no other antibody deficiencies.

Innate immune system: the first defense against pathogens; this part of the immune system does

not require additional "training" to protect. It includes the skin, mucous membranes, cells (leukocytes, natural killer cells, phagocytes), enzymes, and complement.

Acquired immune system: the memory system; this part of the immune system activates if the innate immune system is not able to destroy the pathogen. It includes T-lymphocytes, B-lymphocytes, antibodies, and cytokines.

Antigens: any substance that causes the body to develop an immune response against that substance (such as viruses, bacteria, cancer cells, toxins or chemicals).

Antibodies: highly specialized protein molecules that fit specific antigens; includes IgG, IgA, IgM, IgD, and IgE.

Immunoglobulin G (IgG): the predominant antibody found in the body, it protects against pathogens the body has been exposed to.

Immunoglobulin A (IgA): antibodies found primarily in mucous membranes and secretions; they protect the respiratory tract and intestines.

Immunoglobulin M (IgM): the first antibodies to respond to an infection.

B-lymphocytes: specialized white blood cells that develop in the bone marrow and produce antibodies.

T-lymphocytes: specialized white blood cells that finish their development in the thymus; they help to attack bacteria and viruses and regulate the immune system.

Leukocytes: white blood cells that help fight disease; they can differentiate into specific types of cells.

Natural Killer cells (NK cells): derived in bone marrow and attack viruses, but do not require the additional "training" that T-cells require; may have a role in preventing cancer.

Phagocytes: a specific type of white blood cell that helps to destroy pathogens.

Complement: a system comprised of 30 blood proteins (mostly produced in the liver) that help to prevent infection and inform the immune system.

Intravenous immunoglobulin replacement (IVIG): intravenous replacement of IgG antibodies collected from donor plasma.

Subcutaneous immunoglobulin replacement (SCIG): subcutaneous replacement of IgG antibodies collected from donor plasma.

Quality of life (QoL): a multidimensional assessment of an individual's physical health, psychological state, degree of independence, social relationships, personal beliefs and their relationship to with their individual environment

Health-related quality of life (HRQoL): a multidimensional assessment of an individual's individual's physical health, psychological state, degree of independence, social relationships, personal beliefs and their relationship to with their individual environment as it relates to their health and well-being.

Summary

This research study sought to explore the impact of a low to moderate intensity exercise program for individuals diagnosed with PID. Due to the lack of research about the impact of exercise on this patient population, this research study provides valuable foundational information. Physical therapists are well-equipped to provide exercise prescriptions and guidance to individuals with a chronic medical condition. This research study can provide a starting point for exercise prescription for individuals diagnosed with PID.

Chapter 2: Literature Review

Introduction to the Chapter

This chapter explores the available literature relating to the impact of exercise on stress, fatigue, and quality of life (QoL) in individuals diagnosed with primary immunodeficiency disease (PID). The focus of this review was to provide background information about PID and discuss critical concepts in exercise immunology, as related to PID.

Historical Overview of the Theory and Research Literature

The primary challenge in composing this chapter was the absence of literature relating to exercise in the PID patient population. While the effect of exercise on a variety of chronic diseases was readily identified throughout the literature, there remains a significant void related to this specific diagnosis. Because of this void, this chapter explored individual concepts in exercise immunology and their potential connections, especially as it relates to PID. There was ample literature investigating the pharmacological interventions for individuals diagnosed with PID, and there is extensive, though inconclusive, literature investigating the impact of exercise on immune function in healthy individuals.

Theory and Literature Specific to the Topic

Introduction to PID

PIDs are a group of rare genetic disorders in which immune system function is impaired. The International Union of Immunological Societies (IUIS) updated their classifications of PID in 2015. The IUIS added 34 new gene defects to their 2013 report, resulting in the identification of at least 300 PID variations (Picard et al., 2015). Immune deficiencies can be classified as

primary or secondary. Primary immune deficiencies are the result of dysfunction of the immune system and have a genetic basis, while secondary immune deficiencies are immune dysfunction due to an environmental factor, such as cancer treatment or medication (Raje and Dinakar, 2015). PID can be caused by a defect in any aspect of immune function, most commonly in the B- or T-lymphocytes, natural killer cells, phagocytes, or the complement system (Burton, Murphy and Riley, 2010). Wood (2012) provided a concise categorization of PIDs: combined immunodeficiencies, antibody deficiencies, complement deficiencies, phagocytic disorders, and defects in innate immunity.

PIDs are inherited, heterogeneous disorders of impaired immune system function which may result in an increased rate and severity of infection, immune dysregulation with autoimmune disease and abnormal inflammatory responses, malignancy, and impaired QoL (Berger et al., 2010; Bonilla et al., 2015). Despite the understanding that PIDs are characterized by a genetic defect, most do not have a clear pattern of inheritance. One theory is that some PIDs are the result of a genetic predisposition, combined with an environmental trigger (Boyle and Buckley 2007).

Diagnosis of most variants of PID remains challenging. While early diagnosis and treatment of PID results in improved outcomes and QoL, many patients go undiagnosed, under-diagnosed, or misdiagnosed (Jolles, 2013; Modell et al., 2014). Awareness of PID, even in the healthcare community, continues to be significantly limited, due to the rare and complex nature of these diseases. Diagnosis is made through a detailed clinical history, family history, physical examination, imaging studies of specific organs, complete blood count, quantitative serum immunoglobulin levels, and evaluation of specific antibody responses to protein and polysaccharide antigens (Fried and Bonilla, 2009). Recurrent pneumonia, ear infections, and

sinusitis are the most frequent presenting symptoms, while gastrointestinal issues, abscesses, autoimmune cytopenias, and pulmonary conditions are also commonly reported (Joshi et al., 2009; Wood, 2012). Even within the specific variants of PID, there is heterogeneity; some patients may present with infrequent and minimal infections, while others present with substantial organ damage or autoimmune complications (Sullivan, Boyle, Nauman, and Carton, 2015). A retrospective study performed by Joshi et al. (2009) found a 10-year survival rate after diagnosis of 93.5%, compared to age, sex, and race-matched controls from the same states; while this study suggested a slight decrease in survival rate, there was no statistically significant association between PID and decreased survival. With ongoing advances in treatment options and improved education leading to earlier diagnosis, the future survival rate is promising.

Historically, there has been a significant delay in the diagnosis of PID, though this has improved in recent years. It is not uncommon for patients to experience a diagnostic delay of seven years, with approximately 20% of patients receiving a diagnosis more than 15 years after symptom onset (Chapel et al., 2008). A retrospective study demonstrated a median interval between onset of symptoms and PID diagnosis of 4.7 years (Joshi et al., 2009). Patients with an onset of symptoms before 1986 had a median delay of 17.5 years, those with onset of symptoms between 1986 and 1996 had a median delay in diagnosis of 6.7 years, and patients with an onset of symptoms after 1996 had a median delay of 2.7 years (Joshi et al., 2009). A worldwide review, conducted by Gathmann et al. (2014), showed a delay of five years for patients diagnosed with Common Variable Immune Deficiency (CVID) before the year 2000, and 4.2 years for patients diagnosed after the year 2000; there was notable variation between countries. Diagnostic delay is linked to significant morbidity, including recurrent pneumonias, structural lung damage, and pulmonary heart disease (Wood, 2009). Improving survival rates and reducing

the diagnostic delay will make a significant impact on improving the health and QoL for individuals diagnosed with PID. Early diagnosis leads to early treatment, which can prevent worsening of infections, organ damage, and autoimmune complications.

History of PID

The recognition of PID is relatively recent in the medical field, with new genetic variations and clinical phenotypes of PID being discovered every year. The development of effective antibiotics for secondary infections is what led to the discovery of immune system defects (Dinakar, 2006). Recognition of PID dates back to 1926, with the diagnosis of ataxia telangiectasia (Raje and Dinakar, 2015), an autosomal recessive disorder affecting multiple body systems, primarily the nervous and immune systems (Blaese, Bonilla, Stiehm, and Younger, 2013). Another PID diagnosis, Wiscott-Aldrich syndrome, was identified in 1937 (Raje and Dinakar, 2015). Wiscott-Aldrich syndrome is a condition caused by a genetic defect on the short arm of chromosome X, resulting in immune dysfunction and thrombocytopenia (Blaese et al., 2013). The discovery of Agammaglobulinemia, in 1952, was a milestone in the field of immunology; Agammaglobulinemia was renamed Severe Combined Immune Deficiency (SCID) in 1970 by the World Health Organization (Raje and Dinakar, 2015). Currently SCID and Agammaglobulinemia are recognized as two separate diseases under the PID umbrella.

Early treatments of immune serum globulin were administered intramuscularly, with the first published report of treatment occurring in 1952 (Berger, 2008). Intravenous preparations of immunoglobulin replacement became licensed in the United States in the early 1980s (Berger, 2008). Immunoglobulin replacement therapies are prepared from the purification of donated blood plasma, using a process to specifically isolate immunoglobulin G (IgG) antibodies (Berger,

2008). Clinical immunology is a new and expanding field of medicine, with new discoveries in genetic variations, technology, and medical management occurring every year.

Estimated Prevalence of PID

There is significant variability in the reported and estimated prevalence of PID, both in the United States, and worldwide. Several electronic patient registries and databases have been implemented to help determine the prevalence of PID variants; the challenge in obtaining accurate data remains, due to significant underreporting and misdiagnosis. Modell et al. (2014) suggested that 1-2% of the population may be affected by a PID (when all types and variations are included). A study by Bonilla et al. (2015) suggested that PID may occur in as many as 1:2,000 live births. This is consistent with a randomized telephone survey, conducted in 2005, and published by Boyle and Buckley (2007), which suggests a population prevalence of PID of 1:1,200 for all ages, and 1:2,000 for children, in the United States. However, a review by Madkaikar and Mishra (2013) proposed an incidence of 1:10,000 live births; the authors excluded the diagnosis of Selective Immunoglobulin A (IgA) Deficiency when calculating incidence, due to its high prevalence and asymptomatic presentation.

In the United States, Selective IgA Deficiency is estimated to be the most common PID, affecting 1 in 300 – 700 individuals, however, it is most likely to go undiagnosed as it is typically asymptomatic (Kobrynski and Mayer, 2011; Bonilla et al., 2015); this suggests the potential for an even higher frequency. Selective IgA deficiency is also more common in population groups of European descent; studies have found a much lower prevalence in Asian populations with a frequency of 1:18,000 (Kobrynski and Mayer, 2011; Bousfiha et al., 2013; Bonilla et al., 2015) making precise estimates a challenge. Wood (2009) suggests a prevalence of 1:25,000 to 1:110,000 in the United Kingdom, for Primary Antibody Deficiency. There is

significant variability in the reported prevalence for CVID, one of the more frequently researched PID variants. Bonilla et al. (2015) referenced an estimated prevalence of 1:30,000 in CVID, while Jolles (2013) reports 1:25,000 to 1:50,000. Sullivan et al. (2015) estimated CVID prevalence to be 1:47,000 to 185,000 in Europe, 1:53,000 in Australia, and 1:7,000 to 127,000 in the United States, demonstrating the variability in different countries. The prevalence estimate for CVID, published by Sadeghi et al. (2015), is consistent with other research, from 1:10,000 to 1:200,000. Stonebraker, Farrugia, Gathmann, Party and Orange (2014) reported a prevalence of CVID ranging from 0.79 to 13.94, per 100,000, in the United States. A prevalence of 0.12 to 11.25, per 100,000, for Agammaglobulinemia in the United States has also been identified (Stonebraker et al., 2014), while other countries report a much lower prevalence for both CVID and Agammaglobulinemia.

Joshi et al. (2009) performed a retrospective cohort study on the epidemiology of PID in a Minnesota county over a 31-year period. The overall incidence, during that time, was 4.6 per 100,000 person-years, with a higher incidence rate noted from 2001-2006 (10.3 per 100,000 person-years). B-cell defects accounted for 78%, combined B- and T-cell defects 11%, phagocytic defects 8%, and complement defects 3%. Of the B-cell defects, 30% were IgA deficiency, 26% IgG Subclass Deficiency, 23% Hypogammaglobulinemia, 15% CVID, 3% Transient Hypogammaglobulinemia of Infancy, and 3% Selective Antibody Deficiency (Joshi et al., 2009).

Bousfiha et al. (2013) used data from multiple studies to develop estimates of PID prevalence throughout the world. The authors calculated an estimated 270,193 patients with PID in the United States. Bousfiha et al. (2013) noted only 2,804 patients were registered through United States Immunodeficiency Network (USIDnet), while 60,364 patients were registered in

worldwide PID data tracking programs. Worldwide prevalence estimates based on data collected from the United States should not be considered an accurate depiction of the worldwide prevalence, given the genetic nature of many PID diseases (Bousfiha et al., 2013).

Most studies relating to the epidemiology of PID are focused on prevalence and diagnostic delay. While there has been limited analysis of race and ethnicity, CVID has been reported more often in whites (Sullivan et al., 2015). In a global survey of patients conducted by Modell et al. (2014), 57% of patients were male and 43% female. There are significant regional differences in age, gender, and specific diagnosis, suggesting an increased prevalence of genetic defects and phenotypical variations.

Treatments in PID

Common treatment options for PID are based on the specific diagnosis, and often includes immunoglobulin (specifically IgG) replacement therapy (intravenous [IVIG] or subcutaneous [SCIG]), bone marrow or hematopoietic stem cell transplantation, prophylactic antibiotics, antimicrobial therapy, and surveillance for autoimmune disorders or malignancies (Herriot and Sewell, 2008; Fried and Bonilla, 2009; Madkaikar and Mishra, 2013; Espanol, Prevot, Drabwell, Sondhi and Olding, 2014). IgG replacement therapy has been shown to increase survival rates and life expectancy, reduce infection frequency and severity, decrease antibiotic usage, and reduce hospital admissions (Wood, 2009; Wood, 2012). The goal of IgG replacement is to ensure that patients have protective levels of antibodies against infections and to maintain adequate minimal trough levels specific to the individual patient (Jolles et al., 2014; Nobre, da Silva Gonzalez, Simão, de Morares Pinto and Costa-Carvalho, 2014). There is variability in infusion frequency; IVIG is often administered once every 3-4 weeks while SCIG may be given daily to weekly (Jolles et al., 2014). IVIG is often administered in the home or in a

clinical setting (such as an infusion center) by trained medical personnel, while SCIG is typically self-administered by the patient in the home setting.

In 2014, Nobre et al. conducted a study to investigate the specific antibody levels of patients with a diagnosis of PID, while receiving IVIG. The study found there was considerable variation in the different lots of each brand of IgG preparation, likely reflecting the heterogeneity of the immune status of the plasma donors. There was no significant variation across the multiple brands tested in the study. Of the 21 patients tested by Nobre et al. (2014), all were found to have protective levels of antibodies for tetanus, measles, and varicella; some had below protective levels for diphtheria. Plasma companies who produce immunoglobulin replacement products have strict standards to ensure minimum protective levels for commonly encountered pathogens.

While extensively tested, IgG replacement does have risks of infusion-related reactions (immediate reactions or anaphylaxis, delayed reactions, or adverse events), and the potential for transmissible diseases encountered through blood and plasma donation, such as hepatitis C or prion diseases (Herriot and Sewell, 2008; Wood, 2012). Infusion-related headaches were the primary complaint from patients receiving IVIG; this adverse reaction was significant enough for many to consider changing to an alternate treatment (Espanol et al., 2014). For SCIG, adverse events at the infusion site are the most common concern (this include site pain, itching, and/or swelling). These issues were reported to have only a low or medium impact on patients and did not cause them to investigate changing treatments (Espanol et al., 2014). A survey conducted by Espanol et al. (2014) found that patients on SCIG were more satisfied with their treatment (83%) as compared to patients on IVIG (69%). Effectiveness and method of treatment may have a significant impact on any research investigating QoL in patients with a diagnosis of PID. Those

not receiving treatment, or receiving suboptimal treatment, may have greater variability in their QoL scores.

PID and QoL

The World Health Organization defines QoL as an

> individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment. (1997, p.1)

An important subset of QoL is health-related QoL (HRQoL). HRQoL is a "multidimensional construct covering physical, emotional, mental, social, and behavioral components of well-being and functioning" (Kuburovic et al., 2014, p. 324). Similarly, Sigstad, Stray-Pedersen and Frøland define HRQoL as "a person's satisfaction or happiness within areas of life that are affected by health or health care" (2005, p.2). Physical health, psychological state, level of independence, social relationships, and environmental context are all critical aspects of HRQoL (Jiang, Torgerson, and Ayars, 2015). HRQoL is not a clearly defined entity which is readily quantifiable. Individuals respond and react differently to illness and chronic disease, both physically and psychologically. Mozaffari et al. (2006) suggested that HRQoL be measured based on the individual patient's perspective about the impact made on their life by their illness or disease.

Having a PID impacts overall health and QoL, especially economic and psychosocial factors, which are often made worse by the delay in diagnosis (Dinakar, 2006; Burton et al.,

2010). A review of HRQoL in patients with PID by Jiang et al. (2015) showed that patients with PID, compared to healthy individuals, have lower scores for general health, higher rates of hospitalization, and increased limitations in daily activities. This review of the literature focused on studies of patients with PID that utilized valid and standardized outcome measures for HRQoL (Jiang et al., 2015). Dinakar (2006) also found patients with PID had a poorer HRQoL compared to healthy individuals, primarily in the areas of physical function, self-esteem, and family activities. A low HRQoL, especially in the Physical Functioning, Social Functioning, and Role Emotional domains on the Medical Outcomes Study, 36-Item Short Form Health Survey (SF-36), was predictive of mortality (Tabolli et al., 2014). Tabolli et al. (2014) performed a longitudinal study on 96 participants (50 male, 46 female; 52 were <50 years of age, while 44 ≥51 years of age) with a diagnosis of CVID; the SF-36 and the General Health Questionnaire (GHQ-12) were used to measure HRQoL. Sigstad et al. (2005) sent questionnaires to patients with PID who were >20 years of age; 55 out of 91 patients responded to the survey (ages 23-76 years). The survey sent by Sigstad et al. (2005) was comprised of four standardized scales (Quality of Life Index, SF-36, Jalowiec Coping Scale, and Nowotny Hope Scale) and one scale designed by the authors (The Resources and Pressures in the Past Scale); the authors also completed individual interviews with the participants. In this study, low QoL scores were linked to unemployment, infections in more than four organs, more than two additional diseases, or more than two specific occurrences of stress in the past 2-3 months (Sigstad et al., 2005).

Fear of exposure to infectious pathogens may limit engagement in social or physical activities at the community level. Risk factors for a low HRQoL in individuals with PID include: chronic lung disease, chronic diarrhea, female, and older age (Tcheurekdjian et al., 2004; Quinti et al., 2012; Tabolli et al., 2014). A cross-sectional study compared 58 adult

patients, with a diagnosis of CVID, to previously published data for United States population norms, for diabetes mellitus and congestive heart failure, using the SF-36 (Tcheurekdjian et al., 2004). In this study, Tcheurekdjian et al. (2004) found that individuals with CVID perceived their HRQoL to be significantly worse that patients with congestive heart failure or diabetes mellitus. This low perception of HRQoL may be related to the low prevalence of PID; patients perceive less social support and increased misunderstanding of their diagnosis. The chronicity of having this type of medical condition, and the potential side-effects of lifetime treatment, can also have an impact on QoL (Aghamohammadi et al., 2011).

It is challenging to assess HRQoL in individuals with PID due to the historical absence of a disease-specific questionnaire. In 2017, Barrow et al. published a Letter to the Editor about the construction and validity testing of the PADQOL-16, a disease-specific HRQoL measure for individuals with a diagnosis of Primary Antibody Immune Deficiency Disorders. In this initial testing, the PADQOL-16 was validated by test-retest and Rasch analysis to measure self-perceived symptoms and well-being that are caused by or related to their PID or treatment interventions (Barrow et al., 2017). To date, studies using generic QoL outcome measures typically demonstrate reduced HRQoL, compared to healthy controls, for individuals with PID; this reduction is often seen in both the physical and psychosocial domains. There are several studies that confirm these findings in both adults and children. Kuburovic et al. (2014) demonstrated that HRQoL in children diagnosed with PID is significantly reduced, especially in the psychosocial domains. There is also an increased risk for anxiety and depression in children diagnosed with PID, as compared to children with juvenile idiopathic arthritis and healthy controls (Kuburovic et al., 2014). This study compared 25 children with PID to 50 children with juvenile idiopathic arthritis and 89 healthy children; standardized outcome measures included the

Pediatric Quality of Life Inventory (PedsQL), the Screen for Child Anxiety-Related Emotional Disorders questionnaire, and the Mood and Feeling Questionnaire (Kuburovic et al., 2014).

Mozaffari et al. (2006) evaluated the HRQoL of 50 children with PID (mean age 12.62 ±3.65 years; 68% male and 32% female) compared to 100 healthy children (mean age 11.04 ±3.3 years) using the PedsQL in a case-control study. The authors found that children diagnosed with PID had poorer perceptions of their health and increased limitations in physical and psychosocial activities, as compared to healthy controls. Zebracki, Palermo, Hostoffer, Duff and Drotar (2004) found that children with PID have similar HRQoL as children with juvenile idiopathic arthritis, but poorer HRQoL, as compared to healthy children; this was more pronounced in the physical function domains. This study compared the Child Health Questionnaire-Parent Report (CHQ-PF50), completed by the parents of 36 children diagnosed with PID, 36 children with juvenile idiopathic arthritis, and 36 healthy children (4 to 18 years of age) (Zebracki et al., 2004). Soresina et al. (2009) investigated HRQoL, using the PedsQL, in 25 children (mean age 11.82 ± 3.73 years) with a diagnosis of X-linked agammaglobulinemia (XLA), and compared the results to a previous study of 231 youth with rheumatic disease, and with 80 healthy, age-matched controls. The children with a diagnosis of XLA had a lower total HRQoL score, as compared to the healthy controls, but better HRQoL outcomes, as compared to children with rheumatic disease.

In 2014, Espanol et al. conducted an online questionnaire to investigate HRQoL of patients diagnosed with PID in 21 countries; there were 300 responses (216 patients and 84 caregivers). The median age was 36.0 years for responding patients, while 9.0 years represented the patients who had a caregiver respond. This study utilized the 12-Item Short Form Health Survey (SF-12), the 10-Item Short Form Health Survey (SF-10), and the EuroQoL 5 Dimensions

outcome measures (Espanol et al., 2014). The SF-12 results were compared to normative data from the United States. Summary scores for individuals diagnosed with PID were lower for both the physical component and for the mental component; the lowest individual score was in the general health category (Espanol et al., 2014). Quinti et al. (2012) conducted an observational, short-term, longitudinal cohort study to investigate HRQoL for patients diagnosed with CVID, using the SF-36, the General Health Questionnaire-12 (GHQ-12), the Toronto Alexithymia Scale (TAS-20), the Physician Global Assessment (PhGA), and Patient Global Assessment (PtGA). There were 96 patients who participated; 50 were male and 46 female, with a mean age of 48.2 ± 17 years; 87.5% of participants were receiving hospital-administered IVIG (Quinti et al., 2012). HRQoL, measured by the SF-36, was significantly lower in individuals with PID as compared to healthy individuals; scores for the mental domain were similar in both groups, while the physical scores were lower in the PID group (Quinti et al., 2012).

Tabolli et al. (2014) conducted an observational, longitudinal, cohort study over a six-year period to assess HRQoL and psychological status of individuals with CVID. Of the 96 participants, 50 were male and 46 were female; the mean age was 48.2 ± 17 years and the mean time since diagnosis was 10.7 years. There was a decreased HRQoL in the physical domains (specifically in the Role Physical and General Health scales of the SF-36). In this study, even though the physical health scales were affected more than the mental health scales, one-third of participants with CVID were at an increased risk for anxiety and depression throughout the duration of the study (Tabolli et al., 2014). Another study investigated the HRQoL, through utilization of the SF-36; there were 36 participants, 15-45 years of age and diagnosed with CVID, who were compared to healthy age- and sex-matched controls (Aghamohammadi et al., 2011). In this study, Aghamohammadi et al. (2011) found a significant decrease in the physical

domain scores and the mental domain scores for the participants with CVID. Participants who had a longer delay in their diagnosis had significantly lower scores on the SF-36. Jörgensen et al. (2014) studied 32 adult participants (13 females and 19 males, with a mean age of 48 years) diagnosed with Selective IgA Deficiency, as compared to healthy age- and gender-matched controls. Participants with Selective IgA Deficiency had a poorer HRQoL as it relates to infection, an increased fear of becoming infected, and a perceived increased susceptibility to infections; these were measured by a study-specific questionnaire, the SF-36, and an infection-related, HRQoL measure using a Likert scale for nine questions (Jörgensen et al., 2014). These results correlated to significantly poorer physical health and decreased, but not statistically significant, HRQoL scores.

Effective management of chronic disease, such as PID, is necessary for reducing healthcare expenses and improving patient HRQoL (Burton et al., 2010). Using the SF-36 and several other QoL outcome measures, Nicolay et al. (2005) determined that HRQOL may be impacted by treatment satisfaction, the presence of significant side-effects, lack of effectiveness of treatment, or low compliance with treatment. Abdou et al. (2009) conducted an open-label protocol study with 10 adult patients (9 females with a mean age of 49 years); the patients were given monthly IVIG infusions for 12 months, then were observed for three months off IVIG. The authors developed a QoL questionnaire for this study, based on the WHO's QoL Instrument; unfortunately, this instrument was not validated or named. There was a significant improvement in QoL scores following monthly treatments, but the improvements were not sustained after treatment was discontinued (Abdou et al., 2009).

While some patients may choose not to proceed with treatments, often due to personal or financial reasons, most patients will choose between IVIG and SCIG treatments (when

appropriate for their diagnosis). There have been several studies that have investigated HRQoL as it relates to a specific treatment choice. Espanol et al. (2014) found that patients who are receiving appropriate IVIG or SCIG treatment for their diagnosis of PID have an improved HRQoL. This was measured through a decline in infection frequency and a reduction in patient fear of the potential for future infections. A systematic review by Abolhassani, Sadaghiani, Aghamohammadi, Ochs and Rezaei (2012) found a significant improvement in QoL, and perception of health, when switching from hospital-administered IVIG to home-administered SCIG. Nicolay et al. (2006) performed a prospective, longitudinal study on HRQoL and treatment satisfaction, with adults diagnosed with PID, in the United States and Canada. The participants included two groups: previously received hospital-administered IVIG or previously received home-administered IVIG. Participants were required to have been treated with IVIG for at least four months; there were total of 44 adults (27 males and 17 females). Nicolay et al. (2006) utilized the SF-36 and the Life Quality Index (LQI), which was developed for PID patients receiving immunoglobulin replacement. The authors found that 81% of participants preferred home-administered SCIG over hospital-administered IVIG, and 90% preferred home-administered treatment over hospital-administered treatment (Nicolay et al., 2006). In the same study by Nicolay et al. (2006), 69% of participants preferred home-administered SCIG over home-administered IVIG, with 92% of this group preferring home-administered treatment.

There is often discussion about which route of treatment is preferred, IVIG or SCIG. While this choice is typically based on patient or physician preference, Berger et al. (2010) found that adults (n=42) and children (n=9) who switched from IVIG to home-administered SCIG, for a period of one year, had a significant improvement in the General Health scale of the SF-36. This was a 12 month, open-label, uncontrolled study using a specific brand of IgG replacement;

participant ages ranged from 3 to 66 years, with 21 males and 30 females (Berger et al., 2010). Results noted by Tabolli et al. (2014) and Quinti et al. (2012) showed no significant difference in HRQoL for patients on IVIG, as compared to those on SCIG. In contrast, Haddad, Barnes, and Kafal (2012) performed a review of literature for studies that investigated HRQoL for patients who switched from IVIG to SCIG; a summary of six studies determined that home-based SCIG resulted in improved perception of general health, increased social and emotional well-being, increased independence, and improved treatment satisfaction. Similarly, Fasth and Nyström (2008) found improved HRQoL in participants who switched from a hospital-based IVIG treatment to a home-based SCIG treatment. This was a 12 participant, phase IV, prospective, open-label study conducted on children diagnosed with PID; the mean age was 10.9 years (range 1.7-17.1 years), and there were 2 females and 10 males who participated (Fasth and Nyström, 2008). A systematic review and meta-analysis of 47 published studies, by Abolhassani et al. (2012), found that SCIG, performed by the patient at home, improved HRQoL in pediatric and adult patients, decreased utilization of healthcare resources, and empowered patients in their own care.

PID and Fatigue

Hajjar, Guffey, Minard, and Orange (2017) published the first observational study investigating the prevalence of fatigue in patients with a diagnosis of PID. Their research study was based on analysis of 2,537 patients with a PID diagnosis, who were registered in the United States Immunodeficiency Network (USIDNET) database. Hajjar et al. (2017) found that fatigue was reported in 25.9% (95% CI 23.7 – 28.3) of patients with primary antibody deficiency (PAD), as compared to 6.4% (95% CI 4.9 – 8.2) of non-PAD patients. Patients with a diagnosis of CVID had the highest prevalence of fatigue; additional factors associated with higher levels of

fatigue included female sex, higher body mass index, depression, bronchiectasis, and autoimmunity (Hajjar et al., 2017). While there were numerous limitations in this study, it does strongly suggest a greater prevalence of fatigue for individuals with a diagnosis of PID.

PID and Exercise

As part of the foundational research for this research study, a preliminary study was launched to investigate exercise perceptions and behaviors in individuals diagnosed with PID. Sowers, Litwin, Lee, and Galantino (2018) collected 264 responses from an online survey of individuals with a diagnosis of PID. While 33.20% (n = 82) of respondents participated in some form of exercise, 36.84% (n = 91) had not participated in exercise for at least one year. The respondents who were exercising were most likely to engage in walking (75.74%, n = 178) or stretching (57.02%, n = 134). Sowers et al. (2018) found that most respondents *strongly agreed* (46.25%, n = 111) or *agreed* (40.83%, n = 98) that exercise decreased their stress level and improved their mental well-being. Respondents in the study also reported that fatigue was the most significant barrier to their participation in an exercise program (86.97%, n = 207). This survey about exercise perceptions and behaviors helped to provide key foundational information that helped to guide the development of this research study.

Cost of PID

There is considerable financial cost associated with a diagnosis of a PID. In addition to the potential for significant time lost from work or need for long-term disability, there is the expense of the treatment. Immunoglobulin replacement is made from pooled donor plasma which goes through extensive chemical safety processes to ensure there are no blood-borne pathogens. The estimated average annual cost, in 2011, for an individual with PID, prior to their

diagnosis, is $138,760 (USD); the estimated annual cost, per patient, post-diagnosis was $60,297 (USD) (Modell et al., 2011). The estimated cost for IVIG treatment, per patient, per year, is approximately $30,000 (Modell et al., 2011). This is dependent on the individual patient dosage and specific brand of immunoglobulin. Boyle & Schalchunes conducted a national survey of individuals with PID in 2008. Based on the survey results, the authors calculated an average annual cost of $29,406 (USD) for IVIG therapy (Boyle & Schalchunes, 2008). Patients who received IVIG therapy had an estimated (conservative) average of $25,300 (USD) in health-related savings, due to the protective effects of the medication (Boyle & Schalchunes, 2008). The comprehensive study by Modell et al. in 2011 gathered responses from 490 physicians, 192 centers, and 64 countries; this provided information on 79,764 patients with suspected or diagnosed PID. Cost analysis relating to PID were: pre-diagnosis 33.9 school or work days missed ($6,195 annual cost per patient) versus post-diagnosis 8.9 days missed ($1,625 annual cost per patient); pre-diagnosis 6.38 episodes of acute infections ($25, 299 annual cost per patient) versus post-diagnosis 1.78 acute infection episodes ($7,115 annual cost per patient) (Modell et al., 2011).

Menzin, Sussman, Munsell and Zbrozek (2014) conducted a retrospective database analysis to investigate the economic impact of infections in patients diagnosed with PID, on IVIG treatment, from 2008-2010. Patients diagnosed with PID were studied for a seven-month period, following the start of IVIG. The sample included 490 patients who had at least one infection (out of a total of 1,742 patients diagnosed with PID, who were receiving IVIG treatment). Menzin et al. (2014) calculated the mean total infection-related medical expenditures to be $11,925 ± $37,498 (USD). Sadeghi conducted research specific to the costs associated with a diagnosis of CVID in 2015. Data was collected from a national PID patient registry in

Iran; a questionnaire was used to identify insurance claim data for all resources used by patients diagnosed with CVID in the database (Sadeshi et al., 2015). The estimated total cost for diagnosed CVID (based on an Iranian population) was the equivalent of $274,200 (USD) annually, per patient. The most significant expense prior to the diagnosis was the hospital cost ($25,000 USD per patient), while post-diagnosis was the medication cost ($40,600 USD per patient) (Sadeghi et al., 2015).

These studies demonstrate the variability in the treatment costs for immunoglobulin replacement therapy. While most insurance companies will cover all, or part, of the medication expense, some patients do not have adequate coverage for this life-long, costly medication. This can place a significant financial burden on an individual, and contribute to increased stress, impacting HRQoL for individuals diagnosed with PID.

Exercise and Immune Function

Overview. The area of research known as exercise immunology is a relatively young field of study. Publications relating to exercise immunology began in the late 19th century, but it took until the mid-1980s before a significant number of studies were published (Nieman, 2000). One of the earliest studies published on exercise immunology was by Larrabee in 1902. This study demonstrated a large increase in neutrophil levels in four Boston Marathon runners, suggesting similarities in blood immune markers between extreme athletes and inflammatory or chronic disease conditions (Nieman, 2007).

Even with the recent surge in publications concerning all aspects of exercise immunology, research has shown inconsistent results regarding exercise and the immune system. Most experts agree human and animal models demonstrate that moderate exercise stimulates the

immune system, while intense exercise depresses immune function, potentially increasing susceptibility to infections (Bøyum et al., 1996; Fleshner, 2000; Romeo, Wärnberg, Pozo, and Marcos, 2010; Gillum, Kuennen, Schneider and Moseley, 2011). Despite different responses to moderate versus intense exercise, both intensities typically result in a transient alteration in lymphocyte, macrophage, and pro- and anti-inflammatory cytokine levels (Gillum et al., 2011). The literature review performed by Gillum et al. (2011) incorporated studies of men versus women, and girls versus boys (participating in cycling, treadmill running, or walking), and male versus female mice (participating in treadmill running or swimming). Even a single, acute event of exercise had the potential to increase cortisol, heart rate, blood pressure, leukocyte count, and cytokine levels (Edwards and Booy, 2013). Despite the variability of evidence relating to specific immune marker function, it is essential to remember that a single marker of immune function is not able to accurately reflect an individual's protection against various pathogens. The critical indicator of immune system health is the overall clinical picture and the incidence, severity, and duration of infections sustained by that individual (Gleeson, 2005).

The current theory used to explain the relationship between exercise and immune function is the Inverted J Hypothesis. This hypothesis suggests that regular, moderate exercise enhances immune function, while sedentary behavior (at one end of the curve) and overtraining (at the other end of the curve) leads to suppressed immune function (Matthews et al., 2002; Gleeson, 2006; Hance, Rogers, Hursting, and Greiner, 2007; Martin, Pence and Woods, 2009; Moreira, Delgado, Moreira and Haahtela, 2009; Kakanus et al., 2010; Romeo et al., 2010). The response of the immune system to physical activity is multifactorial and complex. Factors such as age, health status, exercise duration, exercise intensity, and specific nutrient intake (carbohydrates, glutamine, and vitamins) can all have a significant impact (Romeo et al., 2010).

Support for the Inverted J Hypothesis can be seen in studies which demonstrate that athletes participating in high intensity exercise, specifically endurance training, are more prone to frequent influenza or upper-respiratory tract infections (URTI) of longer duration (Gleeson, 2006). It has been shown, in a review of the literature, that post-exercise dysfunction in the immune system is most significant when exercise is continuous, prolonged (>1.5 hours), moderate to high intensity (55-75% VO_{2max}), and when the athlete is fasting (Gleeson, 2007). There are a multitude of studies demonstrating transient changes in immune markers following exercise; research comparing resting immune function in endurance athletes and non-athletes has not provided evidence that exercise is linked to clinically significant changes in resting immunity (Nieman, 2007). Research performed with elite competitive athletes, in swimming and cycling, identified similar changes in immune cell numbers, but this is not always clinically significant or correlated to an increase in infections (Gleeson and Bishop, 2005). While there are consistent transient changes to immune cell numbers and functions, longitudinal studies involving sedentary individuals participating in exercise programs did not show a significant change in immune markers taken at least 24 hours post-exercise (Gleeson and Bishop, 2005). While these literature reviews present insight into various aspects of exercise and immune function, there remains significant gaps in the literature. Additional studies need to be conducted to determine if the type, frequency, duration, or intensity of exercise has a specific impact on immune function. Additionally, studies need to investigate differences between age, gender, ethnicity, prior fitness level, medical comorbidities, hormone levels, and other potentially confounding variables.

Cellular Impact. There is consistent evidence that exercise does impact the numbers and function of circulating immune cells. These changes vary depending on whether the exercise is acute or chronic, and if it is moderate intensity or high intensity. Studies using exercise have

consistently identified changes in both innate immune function and adaptive immune function (Briinsgaard and Pedersen, 2000; Pedersen and Toft, 2000; Nieman, 2003; DiPenta, Green-Johnson, and Murphy, 2004; Brolinson and Elliott, 2007; Dhabhar, 2014). Innate immunity is the first line of defense against infectious pathogens and is involved in tissue damage, repair, and remodeling. Changes to innate immune function may involve neutrophils, macrophages, dendritic cells, cytokines, and natural killer cells (Walsh et al., 2011). The adaptive immune system becomes activated when a pathogen is present and can provide increased protection against reinfection through memory functions in specific cells. Since there is no memory function in the innate immune system, repeated exposures to a specific pathogen will not strengthen the innate immune response (Walsh et al., 2011). Both acute and chronic exercise have been shown to alter the number and function of cells in the innate immune system. However, there is minimal evidence as to whether these alterations will impact susceptibility to infectious diseases or inflammatory responses (Walsh et al., 2011).

Gleeson (2006) suggests that repeated, intense, prolonged exercise may result in a decrease in the circulating numbers and functional capacities of leukocytes. Leukocytes are white blood cells, consisting of granulocytes (60-70%), monocytes (10-15%) and lymphocytes (20-25%); lymphocytes consist of B-cells, T-cells, and natural killer cells (Gleeson and Bishop, 2005). Adaptive immunity involves lymphocytes through humoral immunity (B-cells, including immunoglobulins A, M, G, D, and E) and cell-mediated immunity (T-cells). Exercise causes a rapid increase in circulating lymphocytes and natural killer cells. Schwindt et al. (2007) suggested that leukocytes can be mobilized after just six minutes of physical activity. This study examined children with asthma (n=14), compared to healthy, age-matched controls (n=14), during a six-minute cycle-ergometer exercise program; the mean age was 13.6 years for each

group (Schwindt et al., 2007). Neves et al. (2009) explored the acute effects of resistance exercise sessions at different intensities on the total leukocytes and lymphocytes in healthy, elderly women. The study included 15 elderly women (mean age 67.5 ± 3.9 years) who performed concentric and eccentric resistance exercise at 50% of one-repetition maximum (two sets of 13 repetitions) and 80% one-repetition maximum (two sets of eight repetitions); all participants were physically independent (Neves et al., 2009). The authors found resistance exercises failed to result in significant suppression of the immune cell markers (blood cortisol, leukocyte count, salivary IgA, and lymphocyte count were measured). Additionally, the authors found that salivary IgA had a transient increase following exercise (as compared to the control session), suggesting a temporary protective response in this group of elderly women (Neves et al., 2009). Despite Neves et al. (2009) finding of a lack of immune suppression following exercise, numerous studies demonstrate that innate immunity is impacted by intense exercise, resulting in a transient increase in natural killer cell activity, suppression of neutrophils (Nieman, 2000; Pedersen and Toft, 2000; DiPenta et al., 2004) and increase in total lymphocytes (DiPenta et al., 2004). This is found in comparison studies between athletes and non-athletes (Nieman, 2000; Gleeson, 2006). Natural killer cells are primarily responsible for destroying virus-infected cells and cancer cells; there is evidence of *in vitro* increases in natural killer cell activity from regular, moderate intensity exercise (Maltseva, Sakharov, Tonevitsky, Northoff and Tonevitsky, 2011).

A review by Brolinson and Elliott (2007) suggested most studies pointed to an increase in natural killer cell activity following high-intensity exercise. Low natural killer cell activity had been linked to an increased risk of infection (DiPenta et al., 2004). From this perspective, both moderate and high intensity exercise can have beneficial effects through the resulting increase in

natural killer cell activity. However, the immune system is complex and involves more than just natural killer cells. Despite some studies showing an increased number of circulating natural killer cells, there is evidence that the function of those natural killer cells may be inhibited, potentially compromising immune function, following high-intensity exercise (Pedersen and Toft, 2000).

While natural killer cells are shown to increase following moderate and high-intensity exercise, acute exercise also results in a transient, biphasic change in the numbers of circulating lymphocytes. These changes are related to both exercise intensity and duration, with exercise intensity having a more significant impact (Walsh et al., 2011). Walsh and colleagues completed a comprehensive review of current research and clinical knowledge to publish their consensus statement regarding the impact of immune function on exercise. A study involving 10 elite male cyclists (mean age 24.2 ± 5.3 years), who trained for an average of 292.5 ± 89.8 kilometers/week, determined that lymphocyte counts had a biphasic response; this response increased significantly from pre- to immediate post-exercise, followed by a decrease below the pre-exercise level. Lymphocyte counts then increased from two hours to eight hours post-exercise and returned to baseline at 24 hours post-exercise (Kakanus et al., 2010). Kakanus et al. (2010) also found that neutrophil counts increased significantly from pre- to immediately post-exercise and at two hours post-exercise, then progressively decreased and returned to baseline levels by 24 hours post-exercise. The increase in neutrophil count was noted to result from acute exercise, and the magnitude of the elevation was related to exercise intensity and duration (Walsh et al., 2011).

Gavrieli et al. (2008) investigated neutrophil function in 23 healthy, adult males (mean age 30.5 ± 4.9 years) after 30 minutes of treadmill running at 75% VO_{2max}, compared to 10

healthy adult males (mean age 32.4 ± 4.2 years), who served as the non-exercise, control group. The authors found decreased neutrophil function 24 hours after high intensity exercise participation; neutrophils are an important initial line of defense against pathogens and are involved in the muscle tissue inflammatory response to acute exercise (Gavrieli et al. 2008). In contrast, a review of the literature completed by Pedersen and Toft (2000), found increased neutrophils following repeated, strenuous exercise. Chronic, prolonged exercise training resulted in decreased cytokine production, another marker of innate immunity (Gillum et al., 2011). Cytokine release is a local response to tissue injury or inflammation, which elicits mobilization of lymphocytes, monocytes, and neutrophils (Gillum et al., 2011). More research needs to be performed to determine the complete impact of acute versus chronic exercise on innate immunity.

The typical redistribution of lymphocytes following exercise is an increase in natural killer cells and a decrease in T-cells (Rowbottom and Green, 2000). T-cells are important in the coordination and regulation of the cell-mediated immune response to pathogens, specifically viral pathogens (Walsh et al., 2011). B-cells will differentiate into memory cells and plasma cells to produce immunoglobulins, antibodies specific to the immune response needed. Both T- and B-lymphocyte function may be sensitive to increased training loads in well-trained athletes undergoing intensified training periods (Gleeson and Walsh, 2012).

Brolinson and Elliott (2007) conclude, in their review of the literature, that T-cell and neutrophil function appears to be reduced following high intensity exercise, though this does not always correlate to clinical presentation of disease or acute infection. In contrast, Beshgetoor, Arrues and McGuire (2004) conducted a study on 19 elite female athletes (in training for running and cycling for an average of 11.7 ± 8.3 years; participants were 41.0 ± 4.3 years of age)

compared to 20 age-matched (mean age of 42.0 ± 3.6 years), non-athlete controls. The authors found that T-cell mediated immune function was not significantly impacted by the exercise training programs; the athletes and non-athletes had similar numbers of total circulating lymphocytes (Beshgetoor et al., 2004). A review of the literature by Gleeson (2007) suggested that acute, prolonged, strenuous exercise inhibits the production of immunoglobulins, potentially increasing infection susceptibility. However, a consensus statement by Walsh et al. (2011) reports that serum immunoglobulin is typically unchanged, or slightly increased, in response to brief or prolonged exercise.

A literature review by Rowbottom and Green (2000) found the majority of studies that have investigated serum IgG levels, pre- and post-exercise, have seen no significant change, or a slight increase in IgG levels. The level of serum IgG is critically important for patients with a diagnosis of PID, especially those who are on some form of IgG replacement. Bøyum et al. (1996) conducted an army ranger training course on trained cadets (age range 21-27 years old) in the Norwegian Military Academy. This program utilized strenuous exercise (continuous physical activity of a mean of 35% VO_{2max} and calorie consumption of 35,000 to 40,000 kJ per 24 hours) lasting five to seven days, combined with sleep deprivation (two to three hours permitted during the course), and calorie deficiency (daily intake <3,000 kJ) (Bøyum et al., 1996). There was no incidence of infection during the training period or during subsequent weeks. The authors did demonstrate statistically significant reductions in IgG (6-7% decrease on days three and six), IgM (20-35% decrease from day one to six), and IgA (10-20% decrease from day one to six). The literature review by Rowbottom and Green (2000) showed the potential for exercise and extreme stress to impact serum immunoglobulin levels; preventing a decline in serum immunoglobulin levels in individuals with PID is critically important. However, the

results of this study apply to an extreme situation of stress and exercise requirements, which is not likely to be representative of a controlled, low-to-moderate intensity exercise program. Pershin, Geliev, Tolstov, Kovalchuk and Medvedev (2002) suggested the majority of post-exercise secondary immunodeficiencies are actually related to metabolic disorders, caused by insufficient nutrients (carbohydrates, proteins, vitamins, lipids, minerals, and micronutrients). Nutritional deficiency, as opposed to exercise level, could be a potential cause of the lowered immunoglobulin levels in the study completed by Rowbottom and Green (2000).

A literature review by Pershin et al. (2002) cited several studies of elite athletes in multiple sports in which there was a secondary immunodeficiency with declines in serum IgA, IgG, IgG subclasses, and IgM levels, post-competition. On average, it took 21 to 27 days for the athletes to return to their baseline Ig levels (Pershin et al., 2002). The results from these studies are potentially concerning for a population which is already immunodeficient and on immunoglobulin replacement therapy. However, a more recent, randomized-controlled study by Campbell et al. (2008) included 115 post-menopausal women; the study compared a 12-month aerobic exercise (n = 53, mean age 60.5 ± 7.0 years) versus stretching program (control, n = 62, mean age 60.9 ± 6.8 years) to investigate *in vitro* immune function. Participants were considered overweight or obese, in otherwise good health, and sedentary, prior to the study. Over the course of the study, the exercise intervention progressed to 45 minutes of moderate intensity exercise, five days per week, starting at 40% observed maximal heart rate (16 minutes per session) and ending at 60-75% observed maximal heart rate (for 45 minutes per session) using a treadmill, stationary bicycle, and resistance exercise; the control group consisted of stretching for 60 minutes, one day per week. The authors found no significant differences between the groups (natural killer cell toxicity and T-lymphocyte proliferation) at three and 12 months (Campbell et

al., 2008). Campbell et al. (2008) concluded there was no significant effect of aerobic exercise on overall immune function. Additionally, there was no significant difference for IgG, IgM, or IgA levels between the exercise and stretching groups at 12 months (Campbell et al., 2008). The findings from this research study are valuable, as they suggest a moderate intensity, controlled exercise program will not significantly alter immune function or immunoglobulin levels.

A large cohort study, conducted by Gleeson et al. (2011b), completed with 80 healthy university students, involved in athletics, showed that secretory IgA concentration and secretion rate, circulating B-cells, and natural killer cells are lower in women than men, in an athletic population (Gleeson et al., 2011b). Of the 80 participants who completed the study, 34 were female (mean age 22.1 ± 4.0 years) and 46 were male (mean age 22.9 ± 4.1) (Gleeson et al., 2011b). The participants maintained weekly training logs and completed questionnaires concerning infection incidence. Male athletes completed an average training load of 9.7 ± 4.7 hours per week, while female athletes engaged in an average training load of 8.7 ± 3.8 hours per week; athletes were active on campus in endurance-based sports, such as running, cycling, swimming, triathlon, team games, and racquet-sports (Gleeson et al., 2011b).

Transient changes in immune function, following acute exercise, will typically return to pre-exercise levels within a three to 24-hour period (Nieman, 2000; Gleeson, 2006; Gleeson, 2007; Gleeson and Walsh, 2012). In contrast, prolonged periods of intense training may prevent this recovery period from occurring. This may result in a chronic decrease in immune cell function, though the clinical significance of this has not yet been determined (Walsh et al., 2011). In their review of the literature, Gleeson and Williams (2013) suggested that intensive, chronic training regimens do not allow for sufficient recovery periods, and may result in a chronic suppression of immune function.

The importance of the change in circulating immune cells is unclear. Unfortunately, many studies do not account for changes in blood volume relating to dehydration with prolonged, intense exercise or immune cells not actively in the blood circulation. Additionally, transient changes in cell numbers may not automatically change the function of the available cells (Rowbottom and Green, 2000). In addition to the potential inaccuracy of blood levels of immune function (not all immune cells are freely circulating in the blood), exogenous factors can have a significant impact on immune function. Age, pathology, medications, smoking, alcohol consumption, nutrition, psychological stress, and physical activity may all impact immune system function (Shinkai, Konishi, and Shephard, 1997), and this impact may vary considerably between individuals. Nagatomi (2006) emphasized that it is not proven that a change in cell count will result in a direct impact on physiology and clinical symptoms. There may be a transient decline in several types of immune cells, but there is no definitive evidence in the available research literature that there is a corresponding decline in the effectiveness of the existing cells, or the function of the complex immune system, in its entirety.

Secretory IgA. Despite the inconsistency of evidence for immune cell numbers and function, and the incidence of URTI following moderate and high-intensity exercise, there is consistent evidence related to secretory IgA (sIgA). SIgA is a subclass of IgA, and the primary antibody found in mucosal immunity (including the salivary glands, gastrointestinal system, and respiratory system). Low levels of sIgA have been associated with an increased incidence of URTI (Gleeson and Walsh, 2012). Numerous studies have examined the association between measures of immune function and the risk of URTI in athletic and non-exercise populations (Gleeson, 2006; Åkerström and Pedersen, 2007; Moreira et al., 2009; Kakanus et al., 2010). The only consistent finding is a correlation between low sIgA concentrations and an increase in URTI

symptoms (Walsh et al., 20110. Level of exercise intensity has been linked to the concentration of sIgA, with moderate level exercise leading to an increase in sIgA concentration, and intense exercise leading to a decrease in sIgA concentration (Brolinson and Elliott, 2007; Walsh et al., 2011). Rowbottom and Green (2000) identified a decrease in sIgA following high-intensity exercise, and no change with moderate intensity exercise.

In a literature review, Åkerström and Pedersen (2007) found that marathon runners are more susceptible to URTI during hard training and following competitions; the authors hypothesized a correlation between URTI incidence with the decrease in sIgA. Eda et al. (2013) conducted a study which investigated sIgA and skin infection risk, utilizing high-intensity bicycle endurance exercise (75% HR_{max} for 60 minutes). The participants were seven healthy, adult men (mean age 22.3 years). The results of the study were a decrease in sIgA concentration and an increase in staphylococci skin infection risk (Eda et al., 2013). Thomas et al. (2010) examined the effect of supra-maximal exercise (six by eight second sprints, interspersed with 30 second recovery intervals, on a cycle ergometer) on salivary cortisol and sIgA, in 19 healthy female adolescents (mean age 15.5 ± 0.6 years), who were not in a structured exercise program. The authors concluded there was no significant change in sIgA levels pre- and post-exercise (Thomas et al., 2010). These findings may indicate that duration and frequency of exercise can have an important role in sIgA levels following exercise.

To ensure accurate measurement when monitoring sIgA, adequate fluid consumption during exercise is critical to prevent dehydration and maintain saliva flow (Gleeson, Nieman and Pedersen, 2004). While the evidence supports that high intensity exercise results in a decrease in sIgA concentration, regular moderate exercise can increase sIgA in individuals who were previously sedentary (Gleeson and Walsh, 2012). Neves et al. (2009) investigated sIgA in

healthy, elderly women performing resistance exercises, and found a transient elevation in sIgA after resistance exercise, suggestive of the protective effects of exercise.

Shimizu et al. (2007) investigated sIgA in healthy, sedentary, elderly individuals engaged in an exercise program for six months. Of the 125 participants in the exercise group (age range 60-82 years), 51 were male and 74 were female; of the 33 participants in the non-exercise, control group (age range 62-81 years), 11 were male and 22 were female. The exercise group met five days per week, and consisted of stretching, endurance training (30 minutes on a cycle ergometer), resistance training (seven exercises of ten repetitions, beginning the program with one set, ending the program with three sets), and post-exercise stretching. The conclusion was that moderate intensity exercise enhanced sIgA levels in elderly individuals, independent of age or gender (Shimizu et al., 2007). It is hypothesized that a decrease in circulating IgA and sIgA during exercise or periods of elevated stress is associated with increased activation of the hypothalamic-pituitary-adrenal axis and cortisol release (Neves et al., 2009; Walsh et al., 2011). However, a consensus statement published by Walsh et al. (2011) did not identify any correlation between sIgA and cortisol, in response to exercise. Individuals with PID may have baseline decreased or absent levels of IgA. Selective IgA deficiency is a common variant of PID and is typically asymptomatic. The available research presents conflicting evidence about the relationship between IgA and URTI incidence. It is also unlikely that exercise will increase levels of IgA in individuals with PID who are not capable of producing IgA.

Stress and Cortisol Level. Individuals with a diagnosis of PID are under constant stress, both physiological and psychological. Stress is a common denominator in many chronic diseases which require life-long management. Stress can be measured both qualitatively and quantitatively. Most studies investigating stress and exercise utilize cortisol to quantify the

physiological stress level of their participants (Thomas et al., 2010). Cortisol is a glucocorticoid, and the main steroid produced by the adrenal glands; it is important in immune regulation and function (Thomas et al., 2010). It is well established in the literature that high levels of steroid (glucocorticoid) use can decrease immune function (Bøyum et al., 1996). The effect of prolonged, strenuous exercise on immune function is primarily due to increased circulating stress hormones, such as adrenaline, cortisol, growth hormone, and prolactin (Gleeson et al., 2004; Gleeson, 2006). Exercise results in a physiological stress response, which increases circulating cortisol (Dhabhar, 2014). It is hypothesized that an increase in cortisol to pathological levels, while exercising, may lead to a deleterious effect on immune function (Bøyum et al., 1996). Cortisol may also have a delayed effect during the recovery period following exercise (Rowbottom and Green, 2000).

During periods of stress, the body responds with a complex interaction of the endocrine and nervous systems through the hypothalamic-pituitary-adrenal (HPA) and sympathoadrenal (SA) axes. Stress hormones, such as cortisol, have been shown to alter immune cell responses and can cause an imbalance in innate and adaptive immunity (Huang, Zourdos, Jo, and Ormsbee, 2013). The acute increase in cortisol levels from high intensity and long duration exercise can contribute to leukopenia and lymphopenia (Neves et al., 2009). A review conducted by Clow and Hucklebridge (2001) determined the physiological and immune reactions that occur during acute exercise are similar to reactions during acute psychological stress. Likewise, endurance training (chronic exercise) parallels chronic psychological stress. This is significant, as individuals with PID already deal with the psychological stress of a chronic disease. Adding to their already heightened stress level, high-intensity exercise could potentially result in further decline in immune function.

Both physical and psychological stress can result in changes in immune cell distribution. Acute stress may enhance aspects of innate immunity, while suppressing adaptive immunity; chronic stress may suppress immunity by decreasing cell counts and function (Huang et al., 2013). The effects of chronic stress are similar to the effects of high intensity, prolonged exercise. Evidence suggests that changes in circulating cortisol is related to exercise intensity and duration (Thomas et al., 2010). Martin et al. (2009) completed a review of the literature, suggesting moderate intensity exercise induces a level of cortisol that helps to reduce excess inflammation and activate innate immunity. Mura et al. (2014) investigated cortisol levels and QoL in elderly individuals participating in an exercise program. The vigorous exercise group (n=21, 12 males and 9 females, mean age 69.24 ± 3.9 years) participated in a ten minute warm-up, at 60% heart rate reserve (HRR) for 45 minutes of >60% to 84% of HRR, with a cool-down of 10 minutes <60% HRR; the moderate exercise group (n=21, 14 males and 7 females, mean age 70.0 ± 5.3 years) participated in static and dynamic postural control and spine mobility exercises that maintained the heart rate at <50% HRR (Mura et al., 2014). Mura et al. (2014) concluded vigorous exercise and moderate exercise both had a statistically significant increase in blood cortisol (non-pathological) and SF-12 QoL scores, following a 12-week exercise intervention. However, Martin et al. (2009) and Åkerström and Pedersen (2007) found that prolonged, intense exercise created an elevated and prolonged level of cortisol, resulting in an impaired immune response. A key issue of determining exercise parameters lies in determining what level of cortisol is considered pathological, resulting in negative effects to the individual. While acute high volume resistance training resulted in an increased cortisol level, long-term training (greater than two years) lead to a decrease in resting cortisol concentration (Huang et al., 2013). This finding suggests potential adaptation of the body to exercise intensity and duration.

Routine physical activity resulted in a reduction of the levels of cellular markers used to assess systemic inflammation, suggesting that regular exercise has anti-inflammatory effects (Gleeson, 2007). This indicates that long-term exercise interventions may be effective in reducing the systemic inflammatory response (Huang et al., 2013). Nieman et al. (2012) investigated the influence of age, body composition, physical fitness, training habits, systematic inflammation, and metabolic demands on exercise-induced inflammation and innate immune function in a heterogeneous group of trained male cyclists. The authors found that exercise intensity was the best predictor of acute inflammatory response to a two hour exercise program; other measures were not correlated with immune or inflammatory markers. DiPenta et al. (2004) found that serum cortisol levels increased during prolonged exercise and high intensity exercise, then dropped below baseline, approximately two hours after exercise ended.

Any potential increase in physiological or psychological stress is a significant concern for the PID population. Since glucocorticoids can potentially decrease the already impaired immune function of this population, the potential contribution of elevated cortisol levels from exercise must be monitored. Individuals with PID may have autoimmune complications which contribute to systemic inflammation, thus, increasing the importance of monitoring stress and inflammatory levels in this population, during an exercise program.

Vaccination Response. A common issue for those with a diagnosis of PID is a decreased response to vaccination, due to diminished antibody response. Standard testing for PID includes pre- and post-vaccination titers, to determine if there is a specific antibody response to vaccination. Often, this will be diminished or absent in many of the variants of PID. Several studies reviewed by Nieman (2000) indicated antibody response to vaccination is normal in endurance athletes, post-exercise. Gleeson (2006) found moderate exercise training in healthy

young adults does not have an impact on specific antibody response to vaccination. However, a study by Hance et al. (2007) suggests that a training period of eight weeks, prior to vaccination, is necessary to achieve the stimulatory effect of exercise on adaptive immune function (Hance et al., 2007). The majority of the evidence on this topic suggests that exercise can help to improve the immune system response to vaccination. Edwards and Booy (2013) found that chronic exercise and high levels of physical activity are related to improved vaccination responses in elderly adults and that suboptimal vaccine response in normal adults is more likely to improve with acute exercise.

A literature review conducted by Pascoe, Fiatarone Singh, and Edwards (2014) identified 20 studies (nine using acute exercise, 11 using chronic exercise) which investigated the effects of exercise interventions on vaccination response. The evidence from the review by Pascoe et al. (2014) supported that either acute or chronic exercise significantly augments the immune response to vaccination; there is a greater response for older adults (despite immunosenescence, the typical decline in immune response due to aging), and in antigen development for strains with low response to vaccination (immunogenicity). While it is highly unlikely that exercise will improve vaccination response in individuals with PID who have zero specific antibody response to begin with, the question remains as to whether it can bolster the immune system for those who are weak responders. Even a small boost in vaccination response would be highly beneficial for this population.

Infection Incidence. While levels of immune cells, cortisol, and sIgA are important, most individuals with PID are concerned with the risk of acquiring an infection. The majority of research in exercise and infection is related to URTI incidence. While several studies have demonstrated changes in immune cell function and activity during periods of exercise, no studies

have conclusively linked these changes to an increase in infection incidence or illness (Nieman, 2000).

There are numerous reports of increased URTI frequency in athletes, but minimal evidence to support this claim. These studies are not able to methodologically verify if the upper-respiratory symptoms are true infections, a local inflammatory response, or related to another cause (Walsh et al., 2011). Studies that do correlate exercise to URTI typically do so through self-report of symptoms (mucus production, cough, sore throat), not through clinical measures. A literature review by Nieman (2000) showed that several epidemiological studies support the hypothesis that there is an elevated URTI risk during high intensity training, for the one to two weeks following a competitive endurance race, and during periods of over-training. Evidence from this review suggests that moderate and routine training contributes to a protective effect, and reduction in the incidence of URTI, as compared to the incidence in sedentary individuals. Regular, moderate exercise is linked to a reduced incidence of reported infection, as compared to those who are completely sedentary (Gleeson, 2007; Gleeson and Walsh, 2012).

An epidemiological study by Matthews et al. (2002) investigated reported infection incidence and routine physical activity for a total of 547 participants (280 men, with a mean age of 48.8 ± 12.5 years, and 267 women, with a mean age of 47.2 ± 12.2 years). The authors found that high levels of moderate to vigorous exercise was associated with a 20-30% annual reduction in the risk of contracting an URTI, in a non-athletic population (Matthews et al., 2002). A cohort study by Gleeson et al. (2011b), involving university athletic students, found the decrease in sIgA concentration and secretion rate, circulating B-cells, and natural killer cells in women, as compared to men, is not significant enough to alter URTI incidence. Multiple reviews found no significant influence of gender on susceptibility to URTI incidence in athletes (Gleeson et al.,

2011b; Gleeson and Walsh, 2012). Nieman et al. (2000) performed a cross-sectional comparison of 20 elite female rowers (mean age 22.6 ± 0.5 years) with 19 female non-athletes (mean age 24.6 ± 0.8 years). The rowers were participating in 12-13 training sessions per week, each lasting 90-120 minutes. Nieman et al. (2000) found group differences noted in natural killer cell activity and lymphocyte proliferation (both measures were elevated in the rowers, as compared to the non-athletes), but not for other measures of immune function. The number of days with URTI symptoms did not differ between the groups, and blood immune markers were not correlated to URTI (Nieman et al., 2000). Fahlman et al. (2000) found no increase in URTI when investigating the effect of exercise on immune function in active, elderly women. There were 15 women in the exercise group (mean age 76 ± 5 years) and 14 in the control group (mean age 77 ± 6 years). The authors used a ten-week exercise program of walking for 50 minutes, at 70% HRR. Fahlman et al. (2000) found no acute or chronic suppression of immune function resulting in URTI during the ten-week training period.

Nieman et al. (2014) compared a group of runners (n=13, mean age 34.4 ± 2.4 years) to a group of cyclists (n=22, mean age 36.6 ± 1.7 years) during a three-day period of intensified training (2.5 hours per day), during week five of a 12-week training period. The author investigated URTI incidence, muscle damage, inflammation, and innate immune function. Nieman et al. (2014) found a three-day period of intense exercise was associated with significantly more muscle damage and systemic inflammation in the runners, as compared to the cyclists, despite similar exercise volumes. Measures of innate immune function did decrease, however, there were no significant differences between the two groups; URTI incidence did not differ between the groups at 12 weeks (Nieman et al., 2014).

A literature review performed by Moreira et al. (2009) investigated 30 eligible studies on exercise and immune function. The authors concluded that the direct dose-response relationship between exercise load and risk of URTI was not consistent; there was no conclusive evidence that URTI is correlated to exercise intensity, duration, or frequency (Moreira et al., 2009). A consensus statement from Walsh et al. (2011) noted the cause of URTI symptoms in athletes was uncertain, and inflammation from non-infectious causes could contribute to the symptoms. It is recommended that individuals may exercise with common cold symptoms; intense training can begin a few days after symptom resolution, while mild to moderate exercise does not appear to be harmful during the symptomatic period (Nieman, 2003).

It is clear that URTI risk is multifactorial; overtraining, exposure to new pathogens, sleep deprivation, severe stress, malnutrition, and weight loss are significant contributors (Nieman, 2007). Rowbottom and Green (2000) suggested it is reasonable to recommend appropriate exercise interventions, even to those in immunocompromised states, without concern for negative effects on immune function. The majority of the evidence points towards no increase in URTI risk with exercise; some evidence even suggested a protective effect from a moderate intensity exercise program. While individuals with a diagnosis of PID are more susceptible to URTI, the evidence indicates that there is no increased risk in acquiring an URTI through a moderate intensity exercise program.

Information Known

There is significantly more unknown, than known, about the impact of exercise on fatigue, stress, and QoL in a population with a diagnosis of PID. The focus of research related to PID has been on the diagnostic process, pathology, associated complications, pharmaceutical options, and medical management. There is emerging literature concerning the HRQoL in this

patient population, but again, the focus is on the relationship between HRQoL and medical or pharmaceutical management of the condition.

Exercise immunology is another growing field of research, with emphasis on the impact of exercise intensity on immune function. There are numerous studies to draw from, but the evidence is inconsistent. The majority of experimental studies indicate there is a transient alteration in immune cell numbers and function following high intensity, prolonged exercise. Research points towards negative effects from prolonged, high intensity exercise, and potentially protective effects from moderate intensity exercise. What has not been demonstrated in the literature, is a connection between the cellular changes in immune markers and an increased incidence of infection. Furthermore, the research available is largely done using elite level athletes in a competitive sport. This is not generalizable to a non-elite athlete population, much less a chronic disease population. To date, there are no published studies implementing an exercise program in a cohort of individuals with PID. Research utilizing exercise interventions is readily available in the literature on other chronic diseases, such as HIV or cancer, which often represent secondary immunodeficiency conditions. It is not clear that results from those studies can be generalized to the PID population.

Contribution

This research will be the first to utilize an exercise program in a cohort of individuals with PID. New management models for chronic disease encourages patients to become active members of their healthcare team and participate in self-management (Burton et al., 2010). This research will explore the use of a guided home exercise program and determine its effect on fatigue, stress, and QoL. Home-based exercise programs are inexpensive tools that may provide supplementary management of chronic medical conditions and disease symptoms. Exercise has

been shown to have beneficial effects for a number of chronic disease populations; it can improve strength, endurance, and exercise capacity in a variety of diseases without detrimental effects or complications (Kujala, 2006). It is even suggested that exercise be recognized as a medication, due to its potential for significant health benefits and control of specific aspects of chronic disease (Durstine, Gordon, Wang, and Luo, 2013).

As there is no research on the utilization of an exercise intervention in the PID population, this study will also provide important data relating to self-reported infection incidence during the home-based exercise intervention. Individuals with a diagnosis of PID are often fearful about acquiring an infection, and often choose not to utilize local gyms or exercise groups. The evidence suggests that high intensity, prolonged exercise may increase the incidence of URTI symptoms, but that moderate intensity exercise may offer protective effects. If this holds true for individuals with a diagnosis of PID, exercise may become an important aspect of their medical management.

Conclusion

The investigation of the impact of exercise on fatigue, stress, QoL, and infection incidence in the PID population is a novel area of research. Exercise can have significant benefits for chronic disease populations, and it is important to determine what exercise parameters are safe, and beneficial, for the PID population. Exercise has been shown to be effective in key areas for secondary immunodeficiency populations, including HIV and cancer. While high-intensity, prolonged exercise appears to have a greater impact on immune cell number and function, and contributes to elevated physiological stress, moderate intensity exercise seems to provide a level of increased protection for healthy individuals.

Individuals with a diagnosis of PID already suffer from compromised immune function, leaving them at risk for increased infections and autoimmune diseases. If exercise can contribute any level of protection, even to a minimal degree, it would be a cost-effective and convenient supplement to traditional medical management for the PID population.

Chapter 3: Methodology

Introduction to Chapter

This chapter explores the methodology used to complete this research study. The primary investigation was to determine whether low to moderate intensity exercise had an effect on stress, fatigue, and quality of life (QoL) in participants with a diagnosis of primary immunodeficiency disease (PID). This research study sought to understand the lived experience of an individual with a diagnosis of PID and their perceptions about fatigue, stress, QoL, and exercise. This research also explored evidence regarding the potential for adverse events associated with an exercise program, for an individual who is immune-compromised, by tracking infection incidence and need for non-routine medical intervention.

Research Methods

This research study used a mixed methods approach, blending quantitative and qualitative aspects of investigation. The study employed an experimental design, randomized-controlled trial. Participants were randomized into two groups: an exercise intervention group or a control (non-exercise, normal activities) group. The intervention period lasted eight-weeks. Participants in the exercise group completed a semi-customized, home-based exercise program at a low to moderate intensity. Compliance was tracked through the Physitrack exercise program software (Physitrack, 2017) or through an exercise log (Word or printed versions). Participants in the control group were asked to only engage in routine activities, consisting of less than 75 minutes of exercise per week. For the control group, routine physical activities such as walking to work, climbing stairs at home, walking a dog, or performing inconsistent light exercise that was less than 75 minutes per week was acceptable. Data was collected, using standardized

questionnaires, prior to the start of the eight-week intervention or control period, and again, at the end of the eight-week period. In addition to the quantitative data collected, interpretive phenomenology was used to understand the lived experience of the participants in the study. All participants were asked to maintain a journal about their experience during the eight-week period and were interviewed at the completion of the study to discuss their experience and perspectives.

Subjects

Participants were recruited using social media and advertisement at the 2017 Immune Deficiency Foundation national conference in Anaheim, California. The inclusion criteria were: 18 years of age or older; physician diagnosis of a PID; willingness to participate in an eight-week exercise program. The exclusion criteria were: participation in greater than 75 minutes of structured exercise per week, and any medical condition that prevented participation in a low to moderate intensity exercise program (such as, but not limited to, unstable cardiac condition, uncontrolled asthma/breathing condition, or recent acute injury/procedure [such as a fracture or joint replacement] that required restricted activities).

Power Analysis

Determining power from the traditional method of population estimates proved to be challenging for this study. As discussed in chapter two, the population estimates for these rare diseases are quite variable and remain vague. There are no existing studies investigating exercise with the PID population to utilize as a starting point.

Using a recent population estimate by Bousfiha et al (2013), there are an estimated 270,193 individuals with a diagnosis of PID in the United States. This estimate can be used to determine an a priori power analysis. An additional challenge with an a priori power analysis for

this study was the lack of any prior studies to guide the effect size. Using 270,193 as the population, a confidence level of 95%, and a confidence interval of 5%, the required sample size would be 384 participants (Creative Research Systems, 2012). Recruitment of that number of participants is unrealistic for this type of study, especially with limited recruitment resources available.

Another, and likely more accurate, method to determine sample size is to utilize the calculations provided by the developers of the Short Form-36, version 2 (SF-36v2) tool. Maruish (2011) provides the following tables to help determine sample size for experimental studies using two groups. As this study utilizes two groups, with both pre-test and post-test outcome measures, the two tables, listed in Figure 1 (as cited in Maruish, 2011), highlight the potential sample sizes needed for this study. Table 17.1 provides a better test-retest correlation (0.60), though the test-retest correlation (0.40) for Table 17.2 is also considered adequate (Maruish, 2011). The T-score "represents a standardized distribution with a mean of 50 and a standard deviation (SD) of 10, the variability of each scale is constant and therefore does not influence the effect size that is being detected" (Maruish, 2011, p. 281). A five-point T-score is equivalent to 0.5 SD for all domain scales in the SF-36v2 (Maruish, 2011). Using the five-point T-score, and the 0.60 test-retest correlation, a sample size of 43 per group would be necessary for the SF-36v2 Physical Component Summary scale. This is a more realistic goal given the small size of this chronic disease population. The challenge may be in achieving a five-point T-score difference; for the Physical Component Summary score, a two-point T-score difference is considered the Minimally Important Difference for clinical significance. With that in mind, a sample size of 266 per group would be necessary to validate the two-point difference in the Physical Component Summary score.

Table 17.1

Sample Sizes Needed to Detect SF-36v2 Standard (4-Week Recall) or Acute (1-Week Recall) Form SD*-Unit Differences Between Postintervention Scores of Two Experimental Groups With Preintervention Scores as Covariates (Change Score ANCOVA, Retest Correlation = .60)*

	Number of *T*-Score Points Difference			
	1	2	5	10
PCS	1,059	266	43	12
MCS	1,082	271	44	12
PF	1,071	268	44	12
RP	1,059	266	43	12
BP	1,118	280	46	12
GH	1,212	304	49	13
VT	1,184	297	48	13
SF	1,157	290	47	13
RE	1,082	271	44	12
MH	1,184	297	48	13

Note. Sample size requirements for each scale were adjusted by their respective measurement reliabilities. Estimates assume alpha = .05, two-tailed test, power = 80% (Cohen, 1988), and a test-retest correlation of .60.

Table 17.2

Sample Sizes Needed to Detect SF-36v2 Standard (4-Week Recall) or Acute (1-Week Recall) Form SD*-Unit Differences Between Postintervention Scores of Two Experimental Groups With Preintervention Scores as Covariates (Change Score ANCOVA, Retest Correlation = .40)*

	Number of *T*-Score Points Difference			
	1	2	5	10
PCS	1,368	343	57	15
MCS	1,397	350	58	15
PF	1,382	346	57	15
RP	1,368	343	57	15
BP	1,444	362	60	16
GH	1,565	392	65	17
VT	1,528	383	63	17
SF	1,493	374	62	16
RE	1,397	350	58	15
MH	1,528	383	63	17

Note. Sample size requirements for each scale were adjusted by their respective measurement reliabilities. Estimates assume alpha = .05, two-tailed test, power = 80% (Cohen, 1988), and a test-retest correlation of .40.

Figure 1. Sample size recommendations for the SF-36v2. Adapted from *User's manual for the SF-36v2 Health Survey* (3rd ed.) (p.282) by M.E. Maruish (Ed.). Lincoln, RI: QualityMetric Incorporated.

A third option for a priori sample size calculation was performed utilizing the PS Program, Version 3.1.2, to calculate sample size based on known data from a related study (Dupont & Plummer, 1990). A 2016 study by Viallard et al. investigated QoL using the SF-36v2 and treatment with the subcutaneous medication, Hizentra. While this is not an exercise-based intervention, the scores for the SF-36v2 stayed relatively stable pre- and post-treatment. Viallard et al. (2016) found the mean scores for the SF-36v22 Physical Component Summary was 46.4 ± 10.0 at baseline and 46.3 ± 10.0 at follow-up. These scores can be used to help determine the sample size needed for this study, based on the use of the SF-36v2. According to Maruish (2011), the SF-36v2 Physical Component Summary score shows a Minimally Important Difference (MID) of two T-score points. Utilizing an alpha of 0.05 (two-sided) and a power of 0.8, a standard deviation of 10, a between groups difference of two, and a ratio of one control

group participant per one experimental group participant, the sample size would be 393 participants per group.

Given the rarity of the PID diagnosis and the novelty of an exercise study in the PID community, the sample size calculations determined with the SF-36v2 tool is the most reliable choice. Using a sampling estimate provided by an outcome measure with established reliability and validity is a logical choice, given this is the primary outcome measure utilized in this study.

Specific Procedure

Institutional Review Board Approval

This research study was approved by the Institutional Review Boards (IRB) at Nova Southeastern University and Stockton University. An IRB application was first submitted through Stockton University, as the primary IRB. The IRB application was then submitted through Nova Southeastern University as the secondary approver. This research study was also registered at ClinicalTrials.gov with a unique protocol identification of IRB00010183 (see Appendix A).

Participant Recruitment

Participants were recruited through social media, advertisement at the 2017 Immune Deficiency Foundation (IDF) National Conference, posting on the IDF Friends network, and posting on the PI Connect network. The invitation to participate in the research study was shared on several open, and closed, Facebook groups related to PID. Information about participation was also posted on the IDF Friends website and the PI Connect website. Information about the

research study was presented at the IDF National Conference in the *Let's Talk Research: IDF PI CONNECT Live!* session on June 16, 2017.

Participant Screening

Participant screening for inclusion were: 18 years of age or older, a physician diagnosis of a PID (participants were asked to provide a physician letter or medical documentation/report), and a willingness to participate in eight-week exercise program. Participants were excluded if they were actively participating in a structured exercise program for greater than 75 minutes per week and/or if they had any medical condition that would prevent participation in a low to moderate intensity exercise program (such as, but not limited to, unstable cardiac condition, uncontrolled asthma/breathing condition, and/or recent acute injury [such as fracture or joint replacement] which required restricted activities). Screening (based on inclusion/exclusion criteria) was conducted by the primary researcher via email or telephone. Participants who were deemed eligible were then guided through the informed consent process.

Informed Consent

Participants who met the screening criteria were sent the informed consent and protected health information release to review (see Appendix B for copies of the consent and protected health information release). Once the participants confirmed they had adequate time to review the documents, they underwent the informed consent process via telephone. The study procedures, risks, and benefits were explained to each participant by the primary researcher; participants were provided with ample time to have all questions about the study answered. Participants who agreed to consent to the study then signed and initialed all documents and sent them to the primary researcher via scanned forms sent through email or original forms sent via

regular mail. Once consent was voluntarily given by the participant, they were randomized to the exercise intervention group or control group; they were also sent the pre-study outcome measures to complete.

Randomization

For this research study, enrolled participants (based on the inclusion/exclusion criteria) were randomly assigned to the exercise intervention group or the control (no intervention) group. This was done using permuted block randomization, with randomized block sizes of 2, 4, or 6 per block, to ensure equal sample size in the two groups. A free online computer program was utilized to create a permuted block randomization list (Sealed Envelope Ltd., 2017).

Intervention

Pre-intervention Data Collection. Detailed demographic information and initial outcome measures were collected by the primary researcher from all enrolled participants. The demographic information collected included: age (years), age when diagnosed (years), specific diagnosis (type of PID), current treatment (medication name, route of administration, dosage amount, and frequency of dosage), gender, ethnicity, employment status, type of health insurance, and income range (see Appendix C for the demographic data collection form). Participants were asked to recall infection incidence and non-planned medical intervention in the prior eight-week period. For this, the information collected included: number of infections that did not require medical intervention, number of infections that did require medical intervention, number of non-routine (unexpected) medical appointments related to PID to an urgent care, the emergency room, a primary care physician, or to the physician responsible for managing their PID diagnosis. This information was collected in a fillable PDF, a Word document, or a Google

Doc, pending participant preference (see Appendix D for infection and non-routine medical visit data form). The enrolled participants completed the pre-intervention outcome measures, which included: The Short Form-36, version 2 (SF-36v2), Fatigue Impact Scale (FIS), Perceived Stress Scale-10 (PSS-10), Exercise Benefits/Barriers (EBBS) Scale, Self-Efficacy for Exercise (SEE) Scale, Subjective Exercise Experience Scale (SEES). Participants were given the option of completing these surveys electronically (through a fillable PDF, Word document, or Google Doc) or paper format (printed and returned via regular mail). The pre-study (and post-study) outcome measures can be found in Appendix E.

Intervention Data Collection. During the eight-week intervention period, participants completed the SEES on a weekly basis. This was also an opportunity to encourage continued participation in the study as the primary research had a chance to perform a weekly check-in via email with every participant. Participants also tracked infection incidence and/or non-routine medical visits related to their PID, that occurred during the study period. The information collected included: number of infections that did not require medical intervention, number of infections that did require medical intervention, number of non-routine medical visits related to their PID to an urgent care, the emergency room, a primary care physician, and/or the physician responsible for treating their PID diagnosis.

All participants were asked to keep a journal (containing one to two entries per week) about their perspectives and experiences during the eight-week study period. The journal was available electronically through a Google Docs file, accessible to only the primary researcher and specific participant. Alternatively, some participants chose to keep a written journal which was scanned or mailed to the primary researcher at the end of the study period. The participants were asked to spend approximately 5-15 minutes on each journal entry. They were instructed to reflect

about their experience (with the exercise or no exercise program) and their feelings related to their stress and fatigue levels, and their current QoL.

The participants in the exercise program were asked to maintain a record of the duration, frequency, and intensity of the exercises, using the Physitrack software app or website. Alternately, participants were provided with a fillable PDF or Word document for logging their exercise intensity, frequency, and duration. The Borg Rating of Perceived Exertion Scale (Borg RPE), was used to track the perceived intensity of exercise. Participants were educated via email or phone instructions on how to use the scale. They were asked to rate their level of exertion when participating in exercise, with the goal of an RPE of 11-14 during exercise activities.

Weekly reminders (via telephone or e-mail, based on individual preference) were sent to all participants, to encourage compliance with the SEES questionnaire completion, infection and non-routine medical visit tracking, and journal entries.

Post-intervention Data Collection. Upon completion of the eight-week study period, participants completed the post-intervention outcome measures. This included repeating the SF-36v2, FIS, PSS-10, EBBS, SEE, and SEES scales (see Appendix E for the pre/post-study outcome measures). Detailed interviews were conducted by the primary researcher with individual participants (via telephone) at the end of the eight weeks. Grand tour, semi-structured, open-ended questions focused on quality of life, fatigue, stress, and exercise (see Appendix F for specific interview questions). The interviews were audio-recorded with two devices, a Yemeren Digital Voice Recorder and the Voice Recorder and Audio Editor (produced by Tap Media Ltd.) app via an iPad. The audio files were then sent via secure Dropbox link to Weloty Academic Transcription Services (2018) for transcription. The transcriptions completed by Weloty were reviewed by the primary researcher for accuracy. Transcriptions were also sent to all

participants for review; only five participants returned a corrected transcription of their interview.

Data Collection and Storage. The outcome measures utilized in this study were converted to a fillable pdf, a Word document, Google Doc, and paper format. Outcome measures were converted into a single document with no modifications to the original instruments. Participants were able to access and complete these outcome measures either electronically or using paper (depending on individual preference) during the study (pre-study, weekly, and post-study). Participants without electronic access were mailed paper versions of the surveys, along with pre-paid return envelopes to return all surveys at completion of the eight weeks. Participants were asked to maintain their journal entries in an electronic or paper format. Most participants were willing to engage in electronic journals; for these participants, a private Google Docs document was created for their journal. This electronic journal incorporated privacy settings and was only accessible by the individual participant and the primary researcher. The post-study interviews were completed through telephone communication. All electronic documents were kept confidential and were de-identified, using only the participants study identification number. Audio files sent to Weloty Academic Transcription Services were also protected by a confidentiality agreement and were de-identified (no names were recorded during the interview process).

Exercise Intervention Design. Using the Physitrack Exercise Program, participants were provided with a semi-customized plan of acceptable exercises and an expectation of 75 to 150 minutes of moderate exercise per week (based on exercise recommendations made by the American Heart Association [AHA] in 2014). Moderate intensity exercise was defined, using the AHA (2014) standards, as physical activity rated at 11-14 using the Borg RPE, on a scale of

6-20. Low intensity exercise would be any degree of exercise falling below the parameters of moderate intensity exercise. Participants were provided with, and educated in the use of, the Borg RPE scale prior to the start of the exercise intervention via written email instructions and/or telephone communication.

The Physitrack Exercise Program is a web and app (phone or tablet compatible) home-based exercise program software (Physitrack, 2017). This program provides detailed instructions and videos on how to safely complete the prescribed exercises. It also tracks compliance, by allowing participants to record the frequency and duration of the exercises completed (allowing accurate tracking of the participants activity level while participating in the exercise intervention). The exercise program was semi-customized; the primary researcher consulted with each participant about the type of exercises they were interested in, equipment they had access to, and other mobility limitations or need for exercise modifications. Based on that consultation, each participant was provided with 20-40 different exercises they could select from. The exercises were available through the program every day, but participants were guided to select any of the exercises from the list that would help them achieve the 75-150 minutes per week requirement. The exercises made available to the participants included cardiovascular/aerobic activities (such as walking, jogging, elliptical, cycling, and swimming), core stability (Pilates and yoga style activities), weight lifting (free or machine weights for major muscle groups) or stretching and general range of motion (major muscle groups). Most participants selected walking and core stability programs for their exercise intervention (see Appendix G for a sample exercise program).

Post-Study Control Group Intervention Option. Participants who were randomized to the control group were provided the option to engage in the semi-customized exercise program

after they completed the study period. Data was not collected during this time. Participants were provided with access to the Physitrack Exercise Program software, and a semi-customized exercise program based on their individual interests and needs. All control group participants had a minimum of eight weeks access to the exercise program.

Resource Requirements

There were a variety of resources required to complete this study. A subscription to the Physitrack Exercise Program was necessary to guide the home-based exercise program. Since this exercise program is home-based and available electronically (through a computer, tablet, or smartphone), participants were able to complete the intervention in their own home without specialized equipment. Participants were able to download the exercise program to their device or print the exercise program, if they had limited access to a wi-fi connection. No specialized facilities were required to carry-out the outcome measure testing or intervention program.

Stockton University provided a private, locked office with desktop computer for the primary researcher. This office contains a locked file cabinet to permit storage and protection of sensitive and confidential documents. Stockton University also provided email and telephone communication access that allowed routine contact with participants for recruitment, informed consent, weekly follow-up, and post-study interviews. The mail room was available at Stockton University for shipping of materials to the participants. Access to the SPSS computer program, for data analysis, as well as Excel and Word programs, were provided by Stockton University. Access to the End Note computer program, for managing references when preparing manuscripts, was provided by Nova Southeastern University. Stockton University provided junior faculty funding that covered the cost of transcribing the interviews (performed by Weloty Academic Transcription Services) and the purchase of a student license for the NVIVO 11 (QSR

International Pty Ltd., 2015) software program (to allow detailed analysis of the qualitative data). Optum Insight Life Sciences, Inc. (2016) provided a free non-commercial license agreement permitting use of the SF-36v2 for up to 200 uses. Mapi Research Trust (2016) authorized use of the FIS for no cost, with no limitations on number of uses, for the purpose of this research study. The PSS-10, EBBS, SEE, and SEES are all available for use at no additional cost. Adequate time was needed to recruit, screen, and complete the informed consent process with potential participants. Time was also budgeted to make weekly contact with all participants during the study and to complete the in-depth interviews at study completion with each participant. Sufficient time was necessary to enter, analyze, code, and interpret all data collected and to prepare presentations, publications, and copies of the thesis manuscript. Stockton University awarded the primary research a four-teaching credit course release in the fall 2017 semester, through Research and Professional Development Internal Grant Funding, to focus on data collection and analysis.

Reliability and Validity

Short Form-36 Version 2 (SF-36v2)

The SF-36v2 is a well-established generic measure of health status. It is comprised of 36 questions that delivers an "eight-scale profile of functional health and well-being, as well as two psychometrically based physical and mental health summary measures and a preference-based health utility index" (Maruish, 2011, p.3). Based on data collected from a 2009 United States general population survey, the SF-36v2 shows excellent internal consistency for each of the eight scales (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) and two summary scales (Physical Component Summary and Mental Component Summary) (Maruish, 2011). Using a four-week recall

(N=4,024-4,036), the lowest reliability coefficient was found in the scale of General Health (0.82) and the highest reliability coefficient in the scale of Role-Physical (0.96) and summary scale of Physical Component Summary (0.96) (Maruish, 2011). Using a one-week recall (N=1,983-2,047), the lowest reliability coefficient was in the scale of Social Functioning (0.81) and the highest reliability coefficient in the summary scale of Physical Component Summary (0.97) (Maruish, 2011). For the SF-36v2, the Cronbach's alpha coefficients all "exceed the recommended minimum for group-level comparisons" (Maruish, 2011, p. 257), with most of the reliability coefficients in the 0.80 and 0.90 range.

A formal assessment of test-retest reliability was not completed in the 2009 norming survey of the SF-36v2. A subsample of participants did complete the survey twice and were used to provide preliminary data about the test-retest reliability of the SF-36v2 (Maruish, 2011). There was a mean retest interval of 15 weeks and the estimates of test-retest reliability were excellent (none were below 0.60 and only one subscale was below 0.70) with both a four-week and one-week recall (Maruish, 2011). The standard error of measurement (SEM) has been determined for all subscales of the SF-36v2 for four-week and one-week recalls based on the 2009 norming survey. The SEM results (based on the four-week recall) are as follows: Physical Component Summary (2.0); Mental Component Summary (2.7); Physical Functioning (2.5); Role-Physical (2.0); Bodily Pain (3.6); General Health (4.2); Vitality (3.6); Social Functioning (4.0); Role-Emotional (2.6); and Mental Health (3.6) (Maruish, 2011).

The validity of the SF-36v2 has been extensively evaluated (Maruish, 2011). Construct validity was assessed using factor analysis as described by Maruish (2011), and the Physical Function scale was strongly linked to the physical components and the Mental Health scale was most strongly linked to the mental components. These two components "accounted for more

than 70% of the total variance and more than 80% of the reliable variance in the eight health domain scores" (Maruish, 2011, p.266). Data collected from the 2009 norming survey also supports the predictive validity and content validity (focusing on the domains most significantly impacted by disease or health conditions) (Maruish, 2011).

Fatigue Impact Scale (FIS)

The purpose of the development of the FIS was to better understand the impact of fatigue on quality of life. The outcome measure was validated using participants with chronic fatigue syndrome, multiple sclerosis, and mild hypertension (Fisk et al., 1994). Cronbach's alpha to measure the internal consistency of all FIS items was 0.98 and all subscale items by group was >0.87, indicating excellent construct validity (Fisk et al., 1994). Fisk et al. (1994) completed extensive analysis of the FIS to determine it has excellent external validity, based on the instrument's ability to separate divergent groups based on summary scores and item responses.

Perceived Stress Scale-10 (PSS-10)

Cohen, Kamarck, & Mermelstein (1983) reported on the reliability and validity of the original 14 item PSS scale, based on findings from two studies using college students, and one study using participants in a community smoking-cessation program. The authors determined that age was unrelated to the PSS. The coefficient alpha reliability for the PSS was, respectively, 0.84, 0.85, and 0.86 for the three groups (Cohen et al., 1983). The authors report a test-retest correlation for a two-day period in the college students was 0.85. Cohen et al. (1983) summarized that the PSS has adequate internal and test-retest reliability, and is strongly related to a life-event impact score. The predictive ability of the scale is strongest in the one- to two-month period (Cohen et al., 1983).

The PSS-10 version of the original scale has also been validated. Cohen & Williamson (1988) report factor analysis led to the modification of the original instrument. The PSS-10 was found to have good internal reliability with an alpha coefficient of 0.78 (Cohen & Williamson, 1988). After extensive comparison, Cohen & Williamson (1988) found that correlations between the PSS-10 and other outcomes were equivalent to the original instrument. The authors determined improved factor analysis with the PSS-10, as compared to the original scale; the PSS-10 also shows better internal reliability (Cohen & Williamson, 1988).

Exercise Benefits/Barriers Scale (EBBS)

The EBBS is a 43-item instrument (29-item benefit scale and 14-item barriers scale), designed to measure the perceived benefits and barrier to exercise. The initial psychometric assessment of this outcome measure included item analysis, factor analysis, and reliability measures using a sample of 650 adults (Sechrist, Walker, & Pender, 1987). Sechrist et al. (1987) identified nine factors (five benefits and four barriers) through factor analysis; this explained 64.9% of the variance. Cronbach's alpha reliability coefficients were 0.952 for the total scale, 0.953 for the benefits scale, and 0.886 for the barriers scale. Test-retest reliability was determined from a sample of 63 individuals, with a two-week retest interval. Correlation coefficients were 0.889 for the total scale, 0.893 for the benefits scale, and 0.772 for the barriers scale (Sechrist et al., 1987).

Self-Efficacy for Exercise Scale (SEE)

The SEE scale is a modification of a 1990 unpublished scale to assess self-efficacy barriers to exercise by McAuley (Resnick & Jenkins, 2000). The revision was based on a mixed-methods (quantitative and qualitative) study that investigated a regular walking program for

older adults (Resnick & Jenkins, 2000). Resnick & Jenkins (2000) found an alpha coefficient of 0.92, suggesting excellent internal consistency. The authors note that traditional tests of reliability do not apply, as the SEE scale is "behavior specific and dynamic" (p. 157), so a structured equations approach was used to assess reliability. The squared multiple correlation coefficients ranged from 0.38 to 0.76, with three items below the recommended level of 0.5 (Resnick & Jenkins, 2000). The authors assessed construct and criterion validity through comparison to the Short Form-12. Resnick & Jenkins (2000) found the Short Form-12 scores, when controlled for age and gender, significantly predicted SEE scores ($F=38.9$; $F=24.3$; $F=78.8$).

Subjective Exercise Experience Scale (SEES)

The SEES was developed to measure the subjective response to participation in exercise. Factor analysis identified three key areas, including Positive Well-Being (PWB), Psychological Distress (PD), and Fatigue (McAuley & Courneya, 1994). Preliminary investigation into the psychometric properties of this scale indicate good factorial, convergent, and discriminant validity of the tool (McAuley & Courneya, 1994). McAuley & Courneya (1994) performed factor analysis on the 12-item SEES and found the PWD dimension accounted for 19.6%, the PD accounted for 7%, and Fatigue accounted for 39% of the variation. The authors also determined the internal consistency and found all three scales to have excellent reliability (alpha for PWB = 0.86, PD = 0.85, and Fatigue = 0.88).

Interview and Journal Entries

Reliability can be established by using precise reporting of the interviews, direct quotations from the journal entries, and the use of audio recording devices during interviews for

improved accuracy (Jensen, 1989). Chapter four contains rich, thick narratives from the participant journal entries and the post-study interviews. The interviews employed open-ended questions about stress, fatigue, quality of life, and exercise. The interviews last from 15 minutes to one hour, most lasted 25-30 minutes. To improve accuracy, the interviews were audio recorded using the Yemeren Digital Voice Recorder (a handheld recording device) and the Voice Recorder and Audio Editor (produced by Tap Media Ltd.), an iPad app. The audio files were transcribed by Weloty Academic Transcription Services. The primary researcher verified the transcriptions for accuracy (through comparison of the transcription with the original audio file). Triangulation of data from multiple sources (journal entries and post-study interviews) was performed, and data saturation was achieved. Member checks were performed by sending the completed transcriptions to all participants for review and verification.

Validity is established using a systematic coding and analysis method, triangulation, and research conditions where appropriate information can be obtained (Jensen, 1989). The use of NVIVO software assisted in development a consistent coding system and organizing of the information into themes. The use of journal entries one to two times a week allowed the participants to describe and emphasize their perspectives. All participants were asked to complete a journal about their experience during the study, reflecting specifically about stress, fatigue, and quality of life. Member checks helped to establish credibility; this was done by allowing participants to review the interview transcripts for accuracy (Engward and Davis, 2015). Five participants returned corrections and clarifications of their interview transcriptions. Data was triangulated from the interviews and journal entries to determine key themes.

Two reviewers were involved with the qualitative data and theme development, one was the committee chair for this dissertation, the other was an external reviewer. Both reviewers are

physical therapists with extensive experience in qualitative research involving the concept of QoL.

Chapter 4: Results

Introduction to the Chapter

This research study was designed as a mixed-methods, randomized controlled trial with two groups. Participants were randomized (via permuted block randomization) to either a control group or exercise intervention group. A total of 77 individuals inquired about the research study (refer to Figure 2 for the recruitment and allocation flowchart). The screening questions to determine eligibility were sent to all 77 participants via email; 17 individuals did not return any response to the screening questions. Of the 60 responses to the screening questions, 8 participants were deemed not eligible (they were currently participating in more than 75 minutes of exercise per week). The informed consent was sent to 52 participants; 36 individuals enrolled in the study, while 16 declined to consent to participation. Of the 36 participants, 17 were randomized to the control group and 19 to the exercise intervention group. In the control group, two participants were lost to follow-up and did not complete the final surveys. In the exercise group, one participant dropped out prior to starting the exercise program, due to an unrelated new medical condition; another participant was lost to follow-up and did not complete the final surveys. There was one participant, in each group, that dropped out prior to any data collection, due to reasons unrelated to the study. Data was analyzed for 16 participants in the control group, and 18 participants in the exercise group. Intention-to-treat was followed for analysis of the data; the last observation carried forward was used to address any missing data. Data analysis was performed using SPSS version 20.0 (IBM Corp., 2011) and NVIVO 11 (QSR International Pty Ltd, 2015).

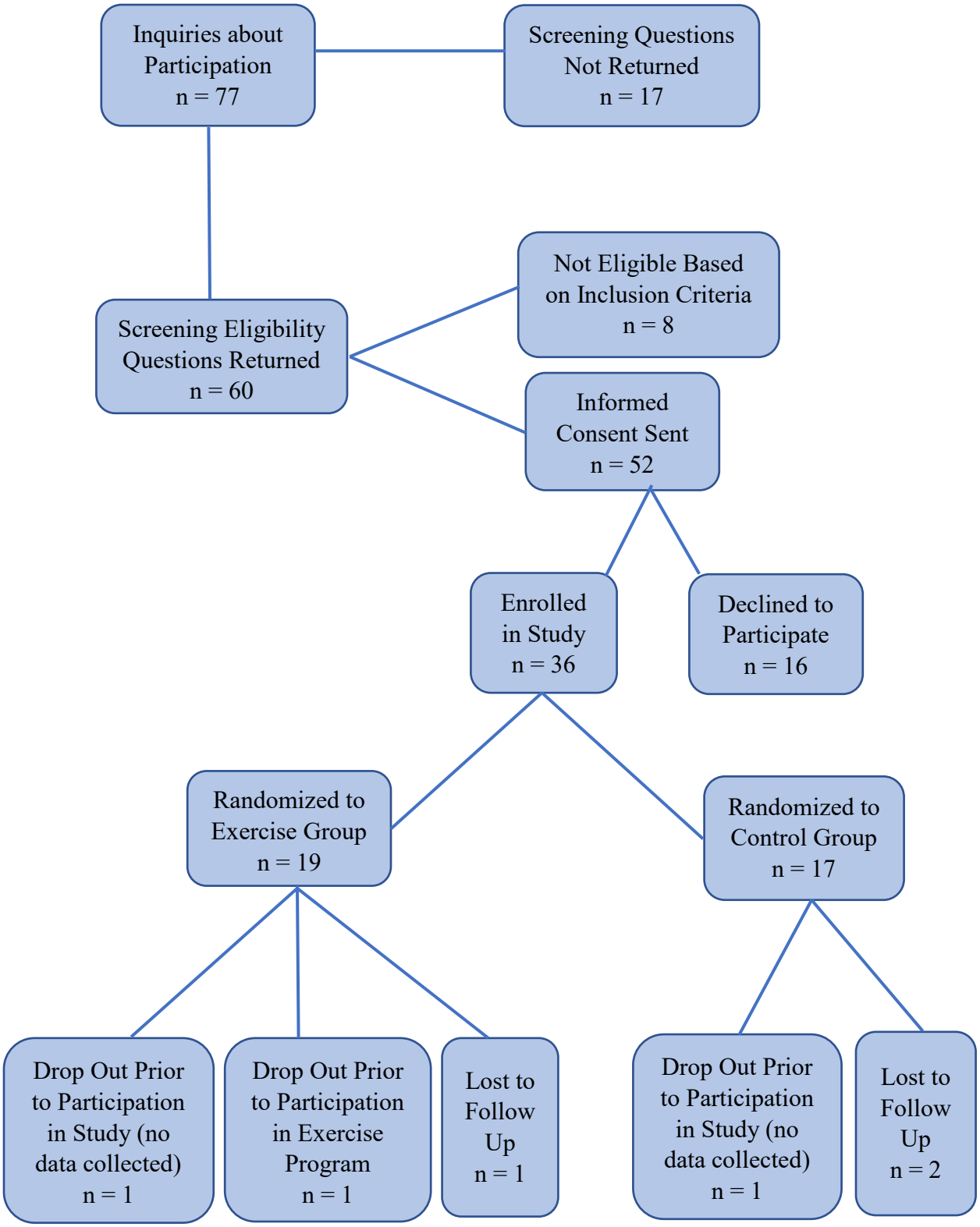


Figure 2. Flowchart of participant enrollment and allocation.

Data Analysis

Quantitative Data

Demographics.

Age. The control group (n = 16) had a mean age of 45.75 years (*SD* = 12.71), and an age range of 22 to 68 years. The exercise intervention group (n = 18) had a mean age of 52.89 years (*SD* = 14.24), and an age range of 22 to 79 years.

Age at Diagnosis. The control group (n = 16) reported a mean age at diagnosis of 38.13 years (*SD* = 12.98), with an age range at diagnosis from 2 to 53 years. The exercise intervention group (n = 18) reported a mean age at diagnosis of 47.67 years (*SD* = 15.21), with an age range at diagnosis from 22 to 78 years.

Type of PID. In the control group (n = 16), 68.8% (n = 11) identified their diagnosis as Common Variable Immune Deficiency (CVID), 12.5% (n = 2) as Hypogammaglobulinemia, 6.3% (n = 1) as Specific Antibody Deficiency (SAD), 6.3% (n = 1) as IgG Subclass Deficiency, and 6.3% (n = 1) as X-linked Agammaglobulinemia (XLA). In the exercise intervention group (n = 18), 72.2% (n = 13) identified their diagnosis as CVID, 16.7% (n = 3) as Hypogammaglobulinemia, 5.6% (n = 1) as SAD, and 5.6% (n = 1) as IgG Subclass Deficiency. This information is presented in Figure 3.

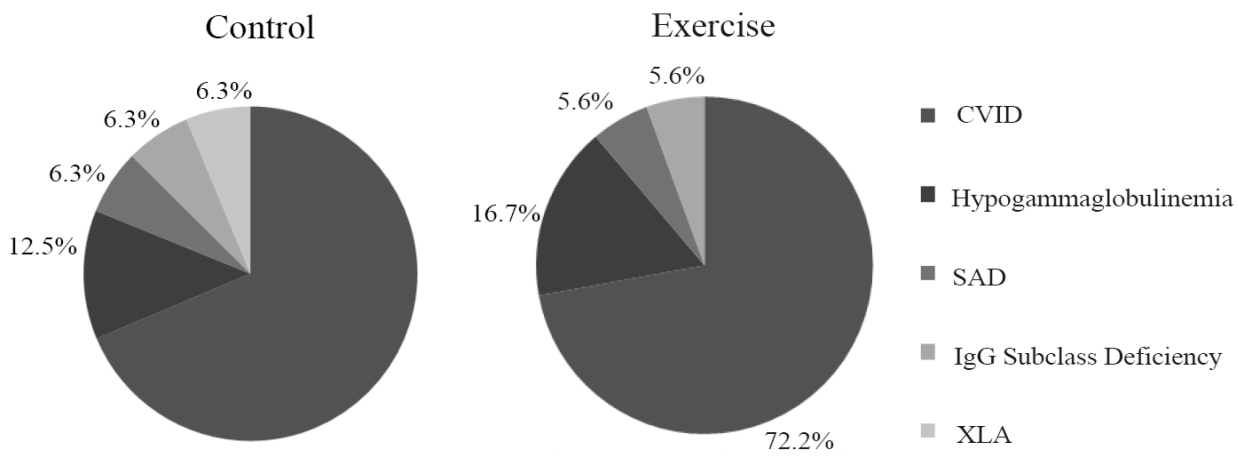


Figure 3. Type of Primary Immunodeficiency Disease.

Physician Responsible for Care. The participants in this study were asked about the physician who is primarily responsible for managing their PID. There were five different physician specialty areas reported. In the control group (n = 16), 56.3% (n = 9) utilized a clinical immunologist, 25.0% (n = 4) utilized an allergist/immunologist, 12.5% (n = 2) utilized their primary care physician, and 6.3% (n = 1) utilized a hematologist. In the exercise group (n =18), 50.0% (n = 9) utilized a clinical immunologist, 33.3% (n = 6) utilized an allergist/immunologist, 11.1% (n = 2) utilized an infectious disease specialist, and 5.6% (n = 1) utilized a hematologist. A graphical representation is presented in Figure 4.

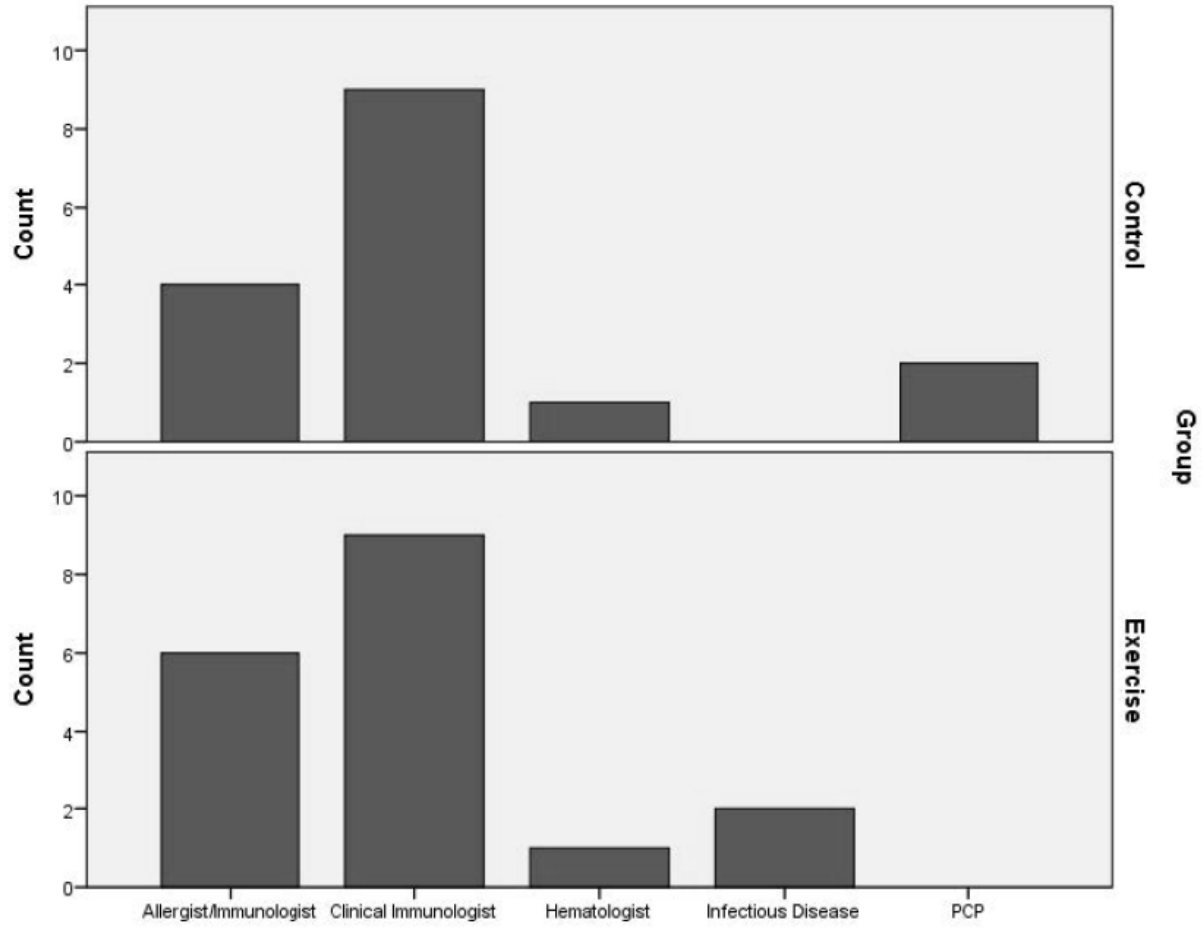


Figure 4. Physician responsible for managing care related to the Primary Immunodeficiency Disease.

Treatment. Four participants (25.0%) in the control group and six participants (33.3%) in the exercise intervention group reported using intravenous immunoglobulin (IVIG) treatment for their PID. Ten participants in the control group (62.5%), and 11 in the exercise intervention group (61.1%), reporting using subcutaneous immunoglobulin (SCIG) to treat their PID. There were two participants in the control group (12.5%) and one participant in the exercise intervention group (5.6%) who were not receiving immunoglobulin replacement (Figure 5).

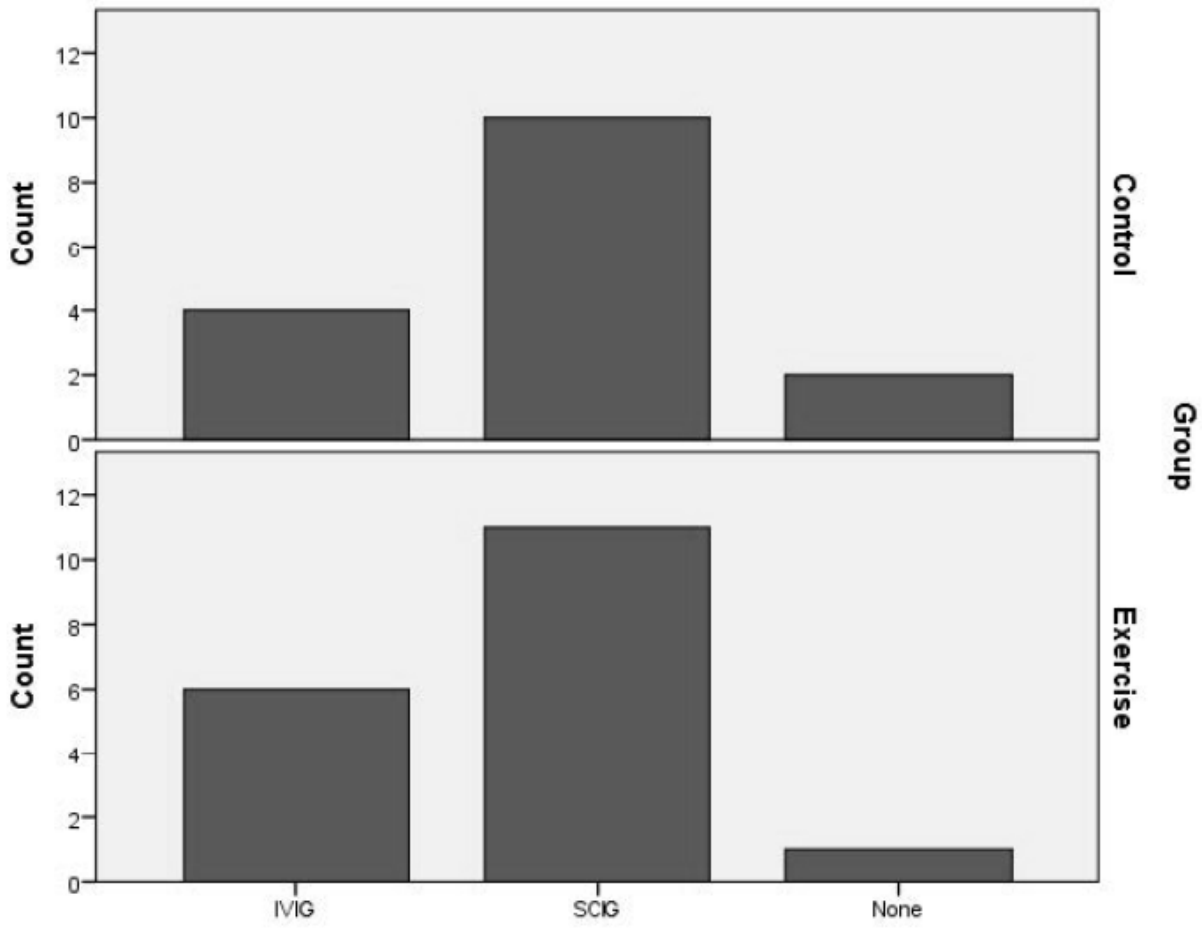


Figure 5. Administration of immunoglobulin replacement for Primary Immunodeficiency Disease.

Participants in both groups reported various brands of immunoglobulin replacement therapy. This is summarized in Table 1.

Table 1

Brands of Immunoglobulin Replacement Therapy

Brand Name	Control Group (%)	Exercise Group (%)
Gamunex-C	2 (12.5%)	2 (11.1%)
Gammagard	1 (6.3%)	2 (11.1%)
Privigen	1 (6.3%)	0 (0%)
Octagam	0 (0%)	2 (11.1%)
Carimune	0 (0%)	1 (5.6%)
Cuvitru	0 (0%)	2 (11.1%)
HyQvia	3 (18.8%)	2 (11.1%)
Hizentra	7 (43.8%)	6 (33.3%)
No Treatment	2 (12.5%)	1 (5.6%)

In addition to using different brands and administration routes, participants also reported different dosages of their immunoglobulin replacement therapy. The control group (n = 16) used an average of 41.62 grams per month (*SD* = 26.04), with a range from 0 to 106.00 grams. This usage of immunoglobulin is similar in the exercise group, where an average of 45.17 grams per month (*SD* = 27.12) were used, with a range of 0 to 130.00 grams. The frequencies for the dosage per month (in grams) in presented in Table 2.

Table 2

Immunoglobulin Replacement Dosage (grams per month).

Dose (per month)	Control Group (%)	Exercise Group (%)
0 g	2 (12.5%)	1 (5.6%)
24 g	0 (0%)	1 (5.6%)
25 g	0 (0%)	2 (11.1%)
30 g	3 (18.8%)	1 (5.6%)
32 g	2 (12.5%)	2 (11.1%)
35 g	0 (0%)	1 (5.6%)
40 g	3 (18.8%)	1 (5.6%)
48 g	2 (12.5%)	3 (16.7%)
50 g	1 (6.3%)	2 (11.1%)
60 g	1 (6.3%)	0 (0%)
64 g	0 (0%)	2 (11.1%)
68 g	0 (0%)	1 (5.6%)
80 g	1 (6.3%)	0 (0%)
106 g	1 (6.3%)	0 (0%)
130 g	0 (0%)	1 (5.6%)

Participants in this study report variety in the frequency of administration of their immunoglobulin replacement therapy. The frequencies for administration are summarized in Table 3.

Table 3.

Immunoglobulin Replacement Therapy Frequency of Administration

Frequency	Control Group (%)	Exercise Group (%)
No Treatment	2 (12.5%)	1 (5.6%)
Twice per Week	1 (6.3%)	2 (11.1%)
Weekly	4 (25.0%)	8 (44.4%)
Twice per Month	2 (12.5%)	0 (0%)
Every Three Weeks	2 (12.5%)	2 (11.1%)
Once per Month	5 (31.3%)	5 (27.8%)

Gender. There was a greater number of female versus male participants, in this study. The distribution was similar across both groups, with 13 females and 3 males in the control group, and 16 females and 2 males in the exercise group (Figure 6).

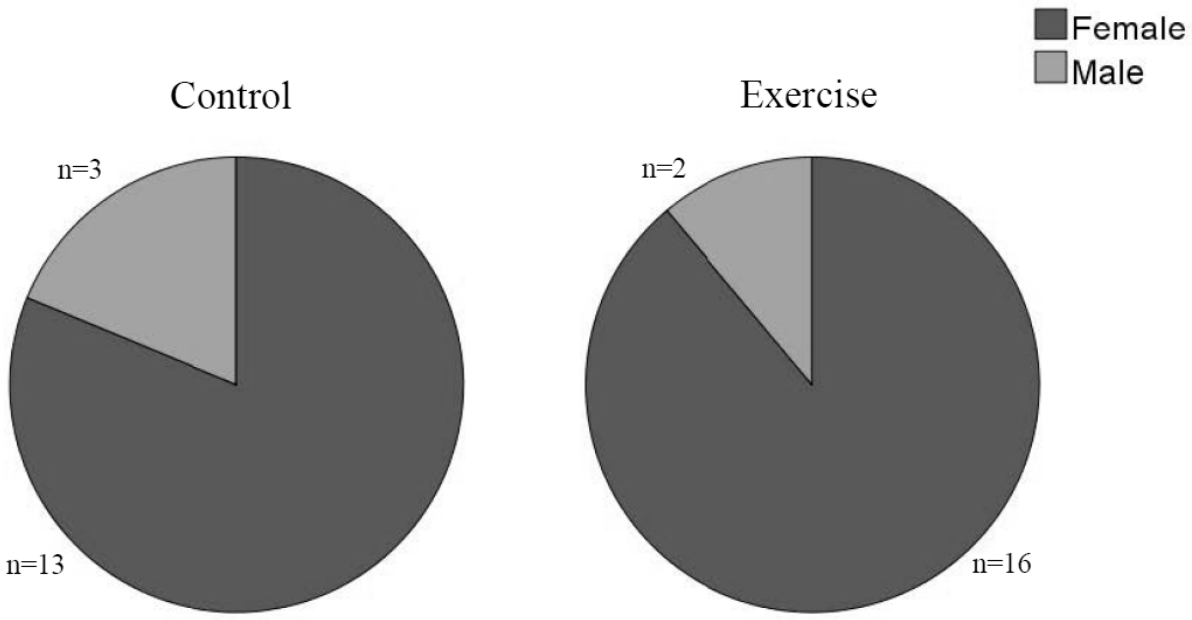


Figure 6. Gender distribution of participants.

Ethnicity. All participants (100%) in the control group (n = 16) identified their ethnicity as White/Caucasian. In the exercise group (n = 18), 16 participants (88.9%) identified their ethnicity as White/Caucasian, while one participant (5.6%) identified as Hispanic/Latino, and one participant (5.6%) identified as other.

Employment. Participants in both groups indicated a variety of employment options. These are summarized in Table 4.

Table 4

Employment Status of Participants

Employment Status	Control Group (%)	Exercise Group (%)
Full-time	5 (31.3%)	5 (27.8%)
Part-time	2 (12.5%)	1 (5.6%)
Disabled	4 (25.0%)	8 (44.4%)
Other	1 (6.3%)	1 (5.6%)
Unemployed	1 (6.3%)	0 (0.0%)
Retired	1 (6.3%)	3 (16.7%)
Student	2 (12.5%)	0 (0.0%)

Health Insurance. Participants in the study reported having access to Medicare, Medicaid, Veterans Benefits (Tricare), or Private Health Insurance. The frequencies are summarized in Table 5.

Table 5

Health Insurance Access of Participants

Health Insurance	Control Group (%)	Exercise Group (%)
Medicare	5 (31.3%)	6 (33.3%)
Medicaid	0 (0.0%)	1 (5.6%)
Veterans Benefits (Tricare)	0 (0.0%)	2 (11.1%)
Private Insurance	11 (68.8%)	9 (50.0%)

Income. Participants were asked to report an income range for their household. A summary of this information is provided in Table 6.

Table 6

Income Range of Participants

Income Range	Control Group (%)	Exercise Group (%)
Greater than $150,000	4 (25.0%)	3 (16.7%)
$100,000 - 149,000	2 (12.5%)	4 (22.2%)
$75,000 - 99,999	1 (6.3%)	4 (22.2%)
$50,000 - 74,999	5 (31.3%)	1 (5.6%)
$35,000 - 49,999	0 (0.0%)	1 (5.6%)
$25,000 - 34,999	2 (12.53%)	3 (16.7%)
Less than $25,000	1 (6.3%)	0 (0.0%)

Exercise Program Compliance. A total of 19 participants were randomized to the exercise group. A semi-customized home exercise program was provided by the primary researcher, based on the individual interests of each participant. The Physitrack Exercise Program, an app and web-based exercise software program, was used to guide participants through their home program. Participants were asked to engage in 75-150 minutes of exercise per week, distributed over three or more days during the week. They were also asked to exercise at a level of 11-14 on the Borg Rating of Perceived Exertion Scale (AHA, 2014).

One participant randomized to the exercise group did not complete the initial surveys and was non-responsive after returning the consent forms. Another participant in this group submitted the initial surveys, but then dropped out prior to engaging in the exercise program due to unrelated medical issues. A third participant in the exercise group was lost to follow-up, despite repeated follow-up requests by the primary researcher. Intention-to-treat analysis was followed for the two participants that had data from the pre-study outcome measures. Of the remaining 16 participants who completed the exercise intervention, two did not maintain a log of their exercise activity. One participant did report attempting to participate in weeks one and two,

which was followed by reported depression about her inability to complete the suggested exercise routine. This participant then reported that she joined a comprehensive exercise, weight management, and motivational program for the last two weeks of the study (she stated that her failure with the exercise intervention motivated her to make some lifestyle changes, and she recognized she needed more comprehensive guidance).

Table 7 summarizes the amount of exercise completed by the individual participants. Several participants had one or two weeks where they did not complete any exercise; primary causes for non-compliance included illness, infusions, and vacations. Several participants exceeded the 150 minutes per week guideline; this is important to consider, as these participants did not have an increased number of infections despite engaging in longer duration of exercise activity. There was inconsistent reporting of the Borg RPE level during the exercise program. Those that did report this measure were noted to have RPE levels between the recommended level of 11-14; occasionally a participant would report a lower value (such as nine) or a higher value (such as 20). Participants did report challenges in completing the exercise program during the summer months due to extreme heat in certain areas of the country and planned vacations.

Table 7

Exercise Adherence (Exercise Intervention Group)

Participant	Total Exercise over 8 Weeks (minutes)	Average Exercise per Week (minutes)	Range (minutes)	Non-Compliance with 75-minute minimum (weeks)
P001	840	105	45 - 180	2/8
P002	569	71	25 - 160	3/8
P005	1028	128	54 - 400	1/8
P008	1275	159	0 - 230	2/8
P009	565	71	0 - 145	3/8
P011	240	30	0 - 120	7/8
P014	2462	308	48 - 477	1/8
P016	1037	130	29 - 200	2/8
P018	Drop-out (ITT)			
P019	2070	259	0 - 430	2/8
P022	765	96	0 - 135	1/8
P023	Not recorded			
P025	867	108	0 - 249	3/8
P027	Drop-out (ITT)			
P029	811	101	0 - 225	4/8
P032	1501	188	145 - 235	0/8
P034	1865	233	150 - 450	0/8
P035	Drop-out (no data)			
P036	Not recorded			

Note. ITT refers to participants analyzed by intention-to-treat (no exercise data collected)

Statistical Analysis

Due to the small number of participants, and non-normal distribution of the pre-study scores and change scores, non-parametric statistical analysis was conducted for all outcome measures. A Mann-Whitney U test was performed for each outcome measure to explore whether there were any significant differences between the control group and the exercise group. This

analysis was conducted using the change scores, to help control for the differences in the pre-study values reported.

Infection Reports.

Infections with No Medical Attention. Participants were asked to recall the number of infections they experienced, that did not require medical attention, during the eight weeks prior to the study period. They were also asked to track the number of infections that did not require medical attention during the eight-week study period. Participants in the control group (n = 16) reported an average of 1.19 infections (*SD* = 1.68) prior to the study, and an average of 1.50 infections (*SD* = 1.75) during the study period. The change score for the control group was an average increase of 0.31 infections (SD = 0.79) during the study period. The range for the control group was 0 to 6 infections for the pre-study period, and for the study period. Participants in the exercise group (n = 18) reported a lower average number of infections in the pre-study period (*M* = 0.33, *SD* = 0.59), and a lower number of infections during the study period (*M* = 0.39, *SD* = 0.70), as compared to the control group. The change score for the exercise group was 0.06 (*SD* = 0.72). The exercise group also had a lower range of reported infections, 0 to 2, for both the pre-study and study periods.

The rank average of the control group was 18.97, as compared to the exercise group which was 16.19. There was no statistically significant difference found between the two groups (*U* = 120.50, *Z* = -0.978, *p* = 0.328), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the rate of infections that did not require medical attention. This can be interpreted as a positive finding, suggesting that the group participating in the exercise intervention did not have significantly more infections than the control group. It suggests that the exercise intervention did not result in an increased

number of infections in the exercise group, as compared to the control group; this related to infections that did not require medical care.

Infections Requiring Medical Attention. Next, participants were asked to recall the number of infections they experienced, in the eight weeks prior to the study, that required medical attention. They also tracked the number of infections during the eight-week study period that required medical attention. Participants in the control group (n = 16) reported an average of 1.38 infections (*SD* = 1.26) requiring medical attention in the pre-study period. The control group reported a slightly lower average of infections requiring medical attention during the eight-week study period (*M* = 1.06, *SD* = 1.18). The average change score for the control group was -0.31 (*SD* = 1.08). Participants in the control group reported a range of infections requiring medical attention of 0 to 5 for the pre-study period, and a range of 0-4 for the study period. Participants in the exercise group reported an average of 1.28 infections (*SD* = 1.70) requiring medical attention in the pre-study period, compared to 1.11 (*SD* = 1.57) during the eight-week study period. The average change score for the exercise group was -0.17 (*SD* = 1.30). The exercise group reported a range of infections requiring medical attention of 0 to 6 for the pre-study period, and 0 to 5 for the study period.

The rank average of the control group was 16.50, as compared to the exercise group which was 18.39. There was no statistically significant difference found between the two groups (*U* = 128.00, *Z* = -0.590, *p* = 0.555), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the rate of infections that did require medical attention. This can be interpreted as a positive finding, suggesting that the group participating in the exercise intervention did not have significantly more infections than the control group. It suggests that the exercise intervention did not result in an increased

number of infections that required medical attention in the exercise group, as compared to the control group.

Urgent Care Visits. Participants were asked to recall the number of urgent care visits that occurred in the eight-week period prior to the study, and to track the number of visits during the eight-week study period. Participants in the control group (n = 16) reported an average of 0.56 urgent care visits (*SD* = 0.89) in the pre-study period, as compared to 0.31 visits (*SD* = 0.48) during the study. The change score for urgent care visits in the control group was -0.25 (*SD* = 0.93). The control group reported a range of 0 to 3 urgent care visits prior to the study period, and 0 to 1 visit during the study period. Participants in the exercise group (n = 18) reported an average of 0.11 urgent care visits (*SD* = 0.32) in the pre-study period, as compared to 0.11 visits (*SD* = 0.32) during the study. The change score for urgent care visits in the exercise group was 0.00 (*SD* = 0.00). The exercise group reported a range of 0 to 1 urgent care visit both prior to, and during, the study period.

The rank average of the control group was 16.44, as compared to the exercise group which was 18.44. There was no statistically significant difference found between the two groups ($U = 127.00$, $Z = -0.731$, $p = 0.465$), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the number of urgent care visits. This can be interpreted as a positive finding, suggesting that the group participating in the exercise intervention did not have significantly more visits to an urgent care facility as compared to the control group. It suggests that the exercise intervention did not result in an increased number of urgent care visits in the exercise group, as compared to the control group.

Emergency Room Visits. Participants were asked to recall the number of emergency room visits that occurred in the eight-week period prior to the study, and to track the number of

visits during the eight-week study period. Participants in the control group (n = 16) reported an average of 0.31 emergency room visits (*SD* = 0.60) in the pre-study period, as compared to 0.13 visits (*SD* = 0.34) during the study. The change score for emergency room visits in the control group was -0.19 (*SD* = 0.54). The control group reported a range of 0 to 2 emergency room visits prior to the study period, and 0 to 1 visit during the study period. Participants in the exercise group (n = 18) reported no emergency room visits (M = 0.00, SD = 0.00) in the pre-study period and during the study period. The change score for urgent care visits in the exercise group was 0.00 (*SD* = 0.00).

The rank average of the control group was 15.81, as compared to the exercise group which was 19.00. There was no statistically significant difference found between the two groups ($U = 117.00$, $Z = -1.515$, $p = 0.130$), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the number of emergency room visits. This can be interpreted as a positive finding, suggesting that the group participating in the exercise intervention did not have significantly more visits to an emergency room as compared to the control group. It suggests that the exercise intervention did not result in an increased number of emergency room visits in the exercise group, as compared to the control group.

Primary Care Physician Visits for Non-Routine Care. Participants were asked to recall the number of PCP visits for non-routine care that occurred in the eight-week period prior to the study, and to track the number of visits during the eight-week study period. Participants in the control group (n = 16) reported an average of 0.94 non-routine PCP visits (*SD* = 1.12) in the pre-study period, as compared to 1.00 visits (*SD* = 2.00) during the study. The change score for non-routine PCP visits in the control group was 0.06 (*SD* = 1.24). The control group reported a range

of 0 to 4 non-routine PCP visits prior to the study period, and 0 to 8 visits during the study period. Participants in the exercise group (n = 18) reported an average of 0.67 non-routine PCP visits (*SD* = 1.03) in the pre-study period, as compared to 0.72 visits (*SD* = 1.96) during the study. The change score for non-routine PCP visits in the exercise group was 0.06 (*SD* = 1.35). The exercise group reported a range of 0 to 3 non-routine PCP visits prior to the study period, and 0 to 8 visits during the study period.

The rank average of the control group was 17.78 as compared to the exercise group which was 17.25. There was no statistically significant difference found between the two groups ($U = 139.50$, $Z = -0.200$, $p = 0.841$), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the number of non-routine PCP visits. This can be interpreted as a positive finding, suggesting that the group participating in the exercise intervention did not have significantly more non-routine visits to their PCP as compared to the control group. It suggests that the exercise intervention did not result in an increased number of non-routine PCP visits in the exercise group, as compared to the control group.

Non-routine Visits to Physician Responsible for Managing PID. Participants were asked to recall the number of non-routine care visits in the eight-week period prior to the study, to the physician who is primarily responsible for managing their PID; they were also asked to track the number of visits during the eight-week study period. Participants in the control group (n = 16) reported an average of 0.56 non-routine visits to the physician who manages their PID diagnosis (*SD* = 1.03) in the pre-study period, as compared to 0.63 visits (*SD* = 1.31) during the study. The change score for non-routine visits to the physician managing their PID diagnosis in the control group was 0.06 (*SD* = 0.77). The control group reported a range of 0 to 4 non-routine

visits to the physician managing their PID diagnosis prior to the study period, and 0 to 5 visits during the study period. Participants in the exercise group (n = 18) reported an average of 0.39 non-routine visits to the physician managing their PID diagnosis (*SD* = 0.85) in the pre-study period, as compared to 0.28 visits (*SD* = 0.67) during the study. The change score for non-routine visits to the physician in charge of managing their PID diagnosis in the exercise group was -0.11 (*SD* = 0.83). The exercise group reported a range of 0 to 3 non-routine visits prior to the study period, and 0 to 2 visits during the study period.

The rank average of the control group was 18.38 as compared to the exercise group which was 16.72. There was no statistically significant difference found between the two groups ($U = 130.00$, $Z = -0.568$, $p = 0.570$), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the number of non-routine visits to the physician responsible for the PID diagnosis. This can be interpreted as a positive finding, suggesting that the group participating in the exercise intervention did not have significantly more non-routine visits to the physician responsible for the PID diagnosis as compared to the control group. It suggests that the exercise intervention did not result in an increased number of non-routine physician visits in the exercise group, as compared to the control group.

SF-36v2.

Physical Function Subscale. The physical function domain is based on a 10-item scale, with three response options. The subscale is intended to measure the presence and degree of physical limitations; low scores indicate significant limitations on the performance of physical activities, while high scores indicate no impairment (Maruish, 2011). For the Physical Function subscale, the control group (n = 16) had a mean pre-study score of 63.75 (*SD* = 28.14), a mean

post-study score of 59.38 (*SD* = 28.98), and a mean change score of -4.37 (*SD* = 11.53). The median (range) of pre-study Physical Function scores for the control group was 65.00 (10.00 to 100.00), the post-study median (range) was 55.00 (5.00 to 95.00), and the median (range) for the change score was 0.00 (5.00 to 45.00). For the Physical Function subscale, the exercise group (n = 18) had a mean pre-study score of 61.67 (*SD* = 19.85), a mean post-study score of 61.67 (*SD* = 18.39), and a mean change score of 0.00 (*SD* = 14.45). The median (range) of pre-study Physical Function scores for the exercise group was 60.00 (30.00 to 90.00), the post-study median (range) was 60.00 (20.00 to 90.00), and the median (range) for the change score was 0.00 (-30.00 to 30.00).

The rank average of the control group was 16.31 as compared to the exercise group which was 18.56. There was no statistically significant difference found between the two groups ($U = 125.00$, $Z = -0.665$, $p = 0.506$), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Physical Function subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores, between the two groups, for the Physical Function subscale of the SF-36v2.

Physical Function T-Score. The Physical Function T-score is a standardized, norm-based score that transforms the Physical Function subscale, so it has a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a Minimally Important Difference (MID)

score of three T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Physical Function T-score, the control group (n = 16) had a mean pre-study score of 43.67 (*SD* = 10.77), a mean post-study score of 41.99 (*SD* = 11.09), and a mean change score of -1.67 (*SD* = 4.41). The median (range) of pre-study Physical Function T-scores for the control group was 44.14 (23.09 to 57.54), the post-study median (range) was 40.32 (21.18 to 55.63), and the median (range) for the change score was 0.00 (-15.32 to 1.92). The exercise group (n = 18) had a mean pre-study Physical Function T-score of 42.87 (*SD* = 7.60), a mean post-study score of 42.87 (*SD* = 7.04), and a mean change score of 0.00 (*SD* = 5.53). The median (range) of pre-study Physical Function T-score for the exercise group was 42.24 (30.75 to 53.71), the post-study median (range) was 42.23 (26.92 to 53.71), and the median (range) for the change score was 0.00 (-11.49 to 11.48).

The rank average of the control group was 16.53, as compared to the exercise group which was 18.36. There was no statistically significant difference found between the two groups ($U = 128.50$, $Z = -0.540$, $p = 0.589$), indicating the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Physical Function T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference, between the two groups, in the Physical Function T-scores of the SF-36v2.

The change score for the Physical Function T-score was -1.67 (*SD* = 4.41) for the control group and 0.00 (*SD* = 5.53) for the exercise group; neither of these meets the MID of three T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study

and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Physical Function T-score is below average for all participants. A below average score indicates that these groups report significant impairment on the performance of physical activities.

Role Physical Subscale. The role physical domain is based on a four-item scale. The subscale is intended to measure physical health role-related limitations; low scores indicate challenges in performing work or activities due to physical limitations, while high scores indicate no impairment (Maruish, 2011). For the Role Physical subscale, the control group (n = 16) had a mean pre-study score of 41.80 (*SD* = 26.78), a mean post-study score of 42.58 (*SD* = 25.84), and a mean change score of -0.78 (*SD* = 18.10). The median (range) of pre-study Role Physical scores for the control group was 46.88 (0.00 to 93.75), the post-study median (range) was 46.88 (0.00 to 87.50), and the median (range) for the change score was 0.00 (-25.00 to 31.25). For the Role Physical subscale, the exercise group (n = 18) had a mean pre-study score of 43.06 (*SD* = 25.26), a mean post-study score of 40.97 (*SD* = 24.08), and a mean change score of -2.08 (*SD* = 15.60). The median (range) of pre-study Role Physical scores for the exercise group was 37.50 (0.00 to 100.00), the post-study median (range) was 40.62 (0.00 to 87.50), and the median (range) for the change score was 0.00 (-25.00 to 31.25).

The rank average of the control group was 18.31 as compared to the exercise group which was 16.78. There was no statistically significant difference found between the two groups ($U = 131.00$, $Z = -0.453$, $p = 0.650$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Role Physical subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores, between the two groups, for the Role Physical subscale of the SF-36v2.

Role Physical T-score. The Role Physical T-score is a standardized, norm-based score that transforms the Role Physical subscale, so it has a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a MID score of three T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Role Physical T-score, the control group (n = 16) had a mean pre-study score of 36.24 (*SD* = 9.62), a mean post-study score of 36.52 (*SD* = 9.28), and a mean change score of 0.28 (*SD* = 6.50). The median (range) of pre-study Role Physical T-scores for the control group was 38.07 (21.23 to 54.91), the post-study median (range) was 38.07 (21.23 to 52.66), and the median (range) for the change score was 0.00 (-8.98 to 11.22). The exercise group (n = 18) had a mean pre-study Role Physical T-score of 36.70 (*SD* = 9.08), a mean post-study score of 35.95 (*SD* = 8.65), and a mean change score of -0.75 (*SD* = 5.60). The median (range) of pre-study Role Physical T-score for the exercise group was 34.70 (21.23 to 57.16), the post-study median (range) was 35.82 (21.23 to 52.66), and the median (range) for the change score was 0.00 (-8.98 to 8.98).

The rank average of the control group was 18.19, as compared to the exercise group which was 16.89. There was no statistically significant difference found between the two groups ($U = 133.00$, $Z = -0.383$, $p = 0.702$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Role Physical

T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference, between the two groups, in the Role Physical T-scores of the SF-36v2.

The change score for the Role Physical T-score was 0.28 (*SD* = 6.50) for the control group and -0.75 (*SD* = 5.60) for the exercise group; neither of these meets the MID of three T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were well below 47, indicating that the Role Physical T-score is below average for all participants. A below average score indicates that both groups report significant impairment on the performance or work or related activities due to physical limitations.

Bodily Pain Subscale. The Bodily Pain domain is based on a two-item scale. The subscale is intended to measure pain intensity and its impact on normal activities; low scores indicate high intensity pain that significantly impacts normal activities, while high scores indicate no pain or activity impairment due to pain (Maruish, 2011). For the Bodily Pain subscale, the control group (n = 16) had a mean pre-study score of 45.50 (*SD* = 19.60), a mean post-study score of 42.00 (*SD* = 16.84), and a mean change score of -3.50 (*SD* = 17.36). The median (range) of pre-study Bodily Pain scores for the control group was 41.00 (12.00 to 84.00), the post-study median (range) was 41.00 (0.00 to 62.00), and the median (range) for the change score was 0.00 (-32.00 to 29.00). For the Bodily Pain subscale, the exercise group (n = 18) had a mean pre-study score of 52.00 (*SD* = 19.46), a mean post-study score of 45.39 (*SD* = 17.13), and a mean change score of -6.61 (*SD* = 14.95). The median (range) of pre-study Bodily Pain scores

for the exercise group was 51.50 (12.00 to 84.00), the post-study median (range) was 46.00 (12.00 to 74.00), and the median (range) for the change score was -10.50 (-31.00 to 23.00).

The rank average of the control group was 18.63 as compared to the exercise group which was 16.50. There was no statistically significant difference found between the two groups (U = 126.00, Z = -0.628, p = 0.530), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Bodily Pain subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, for the Bodily Pain subscale of the SF-36v2.

Bodily Pain T-Score. The Bodily Pain T-score is a standardized, norm-based score that transforms the Bodily Pain subscale, so it has a mean of 50 (SD = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a MID score of three T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Bodily Pain T-score, the control group (n = 16) had a mean pre-study score of 40.02 (SD = 7.90), a mean post-study score of 38.61 (SD = 6.79), and a mean change score of -1.41 (SD = 7.00). The median (range) of pre-study Bodily Pain T-scores for the control group was 38.21 (26.52 to 55.55), the post-study median (range) was 38.21 (21.68 to 46.68), and the median (range) for the change score was 0.00 (-12.91 to 11.69). The exercise group (n = 18) had a mean pre-study Bodily Pain T-score of 42.64 (SD = 7.84), a mean post-study score of 39.98

(*SD* = 6.90), and a mean change score of -2.66 (*SD* = 6.03). The median (range) of pre-study Bodily Pain T-score for the exercise group was 42.44 (26.52 to 55.55), the post-study median (range) was 40.22 (26.52 to 51.51), and the median (range) for the change score was -4.23 (-12.50 to 9.27).

The rank average of the control group was 18.63, as compared to the exercise group which was 16.50. There was no statistically significant difference found between the two groups ($U = 126.00$, $Z = -0.628$, $p = 0.530$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Bodily Pain T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the exercise group, as compared to the control group, in the Bodily Pain T-scores of the SF-36v2.

The change score for the Bodily Pain T-score was -1.41 (*SD* = 7.00) for the control group and -2.66 (*SD* = 6.03) for the exercise group; neither of these meets the MID of three T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Bodily Pain T-score is below average for all participants. A below average score indicates both of these groups report a higher intensity of pain, and that the pain has a significant impairment on normal activities.

General Health Subscale. The General Health domain is based on a five-item scale. The subscale is intended to measure views or expectations of health and health status; low scores indicate a general health status that is poor or declining, while high scores indicate a favorable

outlook on health status (Maruish, 2011). For the General Health subscale, the control group (n = 16) had a mean pre-study score of 26.44 (*SD* = 15.72), a mean post-study score of 24.44 (*SD* = 13.02), and a mean change score of -2.00 (*SD* = 7.74). The median (range) of pre-study General Health scores for the control group was 24.50 (5.00 to 52.00), the post-study median (range) was 23.50 (0.00 to 47.00), and the median (range) for the change score was 0.00 (-20.00 to 10.00). For the General Health subscale, the exercise group (n = 18) had a mean pre-study score of 25.61 (*SD* = 16.05), a mean post-study score of 25.72 (*SD* = 12.51), and a mean change score of 0.11 (*SD* = 11.90). The median (range) of pre-study General Health scores for the exercise group was 25.00 (10.00 to 82.00), the post-study median (range) was 23.50 (5.00 to 52.00), and the median (range) for the change score was 0.00 (-30.00 to 20.00).

The rank average of the control group was 16.28 as compared to the exercise group which was 18.58. There was no statistically significant difference found between the two groups ($U = 124.50$, $Z = -0.679$, $p = 0.497$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the General Health subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, for the General Health subscale of the SF-36v2.

General Health T-Score. The General Health T-score is a standardized, norm-based score that transforms the General Health subscale, so it has a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different

diagnoses and conditions, it is generally accepted that a MID score of two T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the General Heath T-score, the control group (n = 16) had a mean pre-study score of 31.52 (*SD* = 7.48), a mean post-study score of 30.57 (*SD* = 6.19), and a mean change score of -0.95 (*SD* = 3.68). The median (range) of pre-study General Health T-scores for the control group was 30.60 (21.33 to 43.68), the post-study median (range) was 30.12 (18.95 to 41.30), and the median (range) for the change score was 0.00 (-9.51 to 4.75). The exercise group (n = 18) had a mean pre-study General Health T-score of 31.13 (*SD* = 7.63), a mean post-study score of 31.18 (*SD* = 5.95), and a mean change score of 0.05 (*SD* = 5.66). The median (range) of pre-study General Health T-score for the exercise group was 30.84 (23.71 to 57.94), the post-study median (range) was 30.12 (21.33 to 43.68), and the median (range) for the change score was 0.00 (-14.26 to 9.51).

The rank average of the control group was 16.34, as compared to the exercise group which was 18.53. There was no statistically significant difference found between the two groups ($U = 125.50$, $Z = -0.643$, $p = 0.520$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the General Health T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the General Health T-scores of the SF-36v2.

The change score for the General Health T-score was -0.95 (*SD* = 3.68) for the control group and 0.05 (*SD* = 5.66) for the exercise group; neither of these meets the MID of two T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging

from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were well below 48, indicating that the General Health T-score is below average for all participants. The below average scores indicate that these groups report a poor and declining health status compared to normative population data.

Vitality Subscale. The Vitality domain is based on a four-item scale. The subscale is intended to measure subjective feelings of well-being; low scores indicate increased fatigue and exhaustion, while high scores indicate a feeling of having enough energy (Maruish, 2011). For the Vitality subscale, the control group (n = 16) had a mean pre-study score of 37.10 (*SD* = 16.84), a mean post-study score of 37.50 (*SD* = 22.24), and a mean change score of 0.39 (*SD* = 18.18). The median (range) of pre-study Vitality scores for the control group was 37.50 (12.50 to 68.75), the post-study median (range) was 43.75 (0.00 to 81.25), and the median (range) for the change score was 0.00 (-50.00 to 25.00). For the Vitality subscale, the exercise group (n = 18) had a mean pre-study score of 32.64 (*SD* = 21.24), a mean post-study score of 34.03 (*SD* = 21.24), and a mean change score of 1.39 (*SD* = 19.94). The median (range) of pre-study Vitality scores for the exercise group was 31.25 (0.00 to 68.75), the post-study median (range) was 28.12 (6.25 to 75.00), and the median (range) for the change score was 3.12 (-43.75 to 25.00).

The rank average of the control group was 17.03 as compared to the exercise group which was 17.92. There was no statistically significant difference found between the two groups ($U = 136.50$, $Z = -0.262$, $p = 0.793$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Vitality T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant

difference in the scores for the exercise group, as compared to the control group, for the Vitality subscale of the SF-36v2.

Vitality T-Score. The Vitality T-score is a standardized, norm-based score that transforms the Vitality subscale, so it has a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a MID score of two T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Vitality T-score, the control group (n = 16) had a mean pre-study score of 40.53 (*SD* = 8.00), a mean post-study score of 40.72 (*SD* = 10.57), and a mean change score of 0.19 (*SD* = 8.64). The median (range) of pre-study Vitality T-scores for the control group was 40.72 (28.83 to 55.57), the post-study median (range) was 43.69 (22.89 to 61.51), and the median (range) for the change score was 0.00 (-20.80 to 11.89). The exercise group (n = 18) had a mean pre-study Vitality T-score of 38.40 (*SD* = 11.14), a mean post-study score of 39.06 (*SD* = 10.10), and a mean change score of 0.66 (*SD* = 9.48). The median (range) of pre-study Vitality T-score for the exercise group was 37.74 (22.89 to 55.57), the post-study median (range) was 36.26 (25.86 to 58.54), and the range for the change score was 1.48 (-20.80 to 11.89).

The rank average of the control group was 17.13, as compared to the exercise group which was 17.83. There was no statistically significant difference found between the two groups ($U = 138.00$, $Z = -0.209$, $p = 0.834$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Vitality T-

score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the Vitality T-scores of the SF-36v2.

The change score for the Vitality T-score was 0.19 (*SD* = 8.64) for the control group and 0.66 (*SD* = 9.48) for the exercise group; neither of these meets the MID of two T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Vitality T-score is below average for all participants. The below average scores indicate that these groups report a lower subjective perception of well-being, with increased levels of fatigue.

Social Functioning Subscale. The Social Functioning domain is based on a two-item scale. The subscale is intended to measure the impact of physical or emotional issues on social activities; low scores indicate significant interference in normal social activities due to physical or emotional problems, while high scores indicate no impact on normal social activities (Maruish, 2011). For the Social Functioning subscale, the control group (n = 16) had a mean pre-study score of 43.75 (*SD* = 28.87), a mean post-study score of 43.75 (*SD* = 32.27), and a mean change score of 0.00 (*SD* = 13.69). The median (range) of pre-study Social Functioning scores for the control group was 50.00 (0.00 to 100.00), the post-study median (range) was 43.75 (0.00 to 100.00), and the median (range) for the change score was 0.00 (-25.00 to 25.00). For the Social Functioning subscale, the exercise group (n = 18) had a mean pre-study score of 50.69 (*SD* = 28.27), a mean post-study score of 52.08 (*SD* = 33.28), and a mean change score of 1.39 (*SD* = 17.09). The median (range) of pre-study Social Functioning scores for the exercise group

was 50.00 (0.00 to 100.00), the post-study median (range) was 50.00 (0.00 to 100.00), and the median (range) for the change score was 0.00 (-37.50 to 37.50).

The rank average of the control group was 16.66 as compared to the exercise group which was 18.25. There was no statistically significant difference found between the two groups (U = 130.50, Z = -0.490, p = 0.624), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Social Functioning subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, for the Social Functioning subscale of the SF-36v2.

Social Functioning T-Score. The Social Functioning T-score is a standardized, norm-based score that transforms the Social Functioning subscale, so it has a mean of 50 (SD = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a MID score of three T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Social Functioning T-score, the control group (n = 16) had a mean pre-study score of 34.78 (SD = 11.58), a mean post-study score of 34.78 (SD = 12.94), and a mean change score of 0.00 (SD = 5.49). The median (range) of pre-study Social Functioning T-scores for the control group was 37.29 (17.23 to 57.34), the post-study median (range) was 34.78 (17.23 to 57.34), and the median (range) for the change score was 0.00 (-10.03 to 10.02). The exercise group (n = 18) had a mean pre-study Social Functioning T-score of 37.57 (SD = 11.34), a mean

post-study score of 38.12 (*SD* = 13.35), and a mean change score of 0.56 (*SD* = 6.85). The median (range) of pre-study Social Functioning T-score for the exercise group was 37.29 (17.23 to 57.34), the post-study median (range) was 37.29 (17.23 to 57.34), and the median (range) for the change score was 0.00 (-15.04 to 15.04).

The rank average of the control group was 16.72, as compared to the exercise group which was 18.19. There was no statistically significant difference found between the two groups ($U = 131.50$, $Z = -0.452$, $p = 0.651$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Social Functioning T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, in the Social Functioning T-scores of the SF-36v2.

The change score for the Social Functioning T-score was 0.00 (*SD* = 5.49) for the control group and 0.56 (*SD* = 6.85) for the exercise group; neither of these meets the MID of three T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Social Functioning T-score is below average for all participants. The below average scores indicate that these groups report a higher degree of interference in normal social activities due to physical or emotional problems.

Role Emotional Subscale. The Role Emotional domain is based on a three-item scale. The subscale is intended to measure mental health-related role limitations; low scores indicate difficulty with work and other activities due to emotional problems, while high scores indicate

no limitations due to emotional problems (Maruish, 2011). For the Role Emotional subscale, the control group (n = 16) had a mean pre-study score of 68.75 (*SD* = 26.26), a mean post-study score of 75.00 (*SD* = 24.15), and a mean change score of 6.25 (*SD* = 19.84). The median (range) of pre-study Role Emotional scores for the control group was 66.67 (25.00 to 100.00), the post-study median (range) was 79.16 (33.33 to 100.00), and the median (range) for the change score was 0.00 (-25.00 to 50.00). For the Role Emotional subscale, the exercise group (n = 18) had a mean pre-study score of 68.52 (*SD* = 29.78), a mean post-study score of 65.28 (*SD* = 31.73), and a mean change score of -3.24 (*SD* = 21.79). The median (range) of pre-study Role Emotional scores for the exercise group was 75.00 (16.67 to 100.00), the post-study median (range) was 70.84 (8.33 to 100.00), and the median (range) for the change score was 0.00 (-41.67 to 50.00).

The rank average of the control group was 19.47 as compared to the exercise group which was 15.75. There was no statistically significant difference found between the two groups ($U = 112.50$, $Z = -1.128$, $p = 0.259$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Role Emotional subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, for the Role Emotional subscale of the SF-36v2.

Role Emotional T-Score. The Role Emotional T-score is a standardized, norm-based score that transforms the Role Emotional subscale, so it has a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different

diagnoses and conditions, it is generally accepted that a MID score of four T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Role Emotional T-score, the control group (n = 16) had a mean pre-study score of 43.11 (*SD* = 10.97), a mean post-study score of 45.72 (*SD* = 10.09), and a mean change score of 2.61 (*SD* = 8.29). The median (range) of pre-study Role Emotional T-scores for the control group was 42.24 (24.83 to 56.17), the post-study median (range) was 47.46 (28.31 to 56.17), and the median (range) for the change score was 0.00 (-10.44 to 20.89). The exercise group (n = 18) had a mean pre-study Role Emotional T-score of 43.02 (*SD* = 12.44), a mean post-study score of 41.66 (*SD* = 13.26), and a mean change score of -1.35 (*SD* = 9.10). The median (range) of pre-study Role Emotional T-score for the exercise group was 45.72 (21.35 to 56.17), the post-study median (range) was 43.98 (17.87 to 56.17), and the median (range) for the change score was 0.00 (-17.41 to 20.89).

The rank average of the control group was 19.38, as compared to the exercise group which was 15.83. There was no statistically significant difference found between the two groups ($U = 114.00$, $Z = -1.074$, $p = 0.283$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Role Emotional T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the Role Emotional T-scores of the SF-36v2.

The change score for the Role Emotional T-score was 2.61 (*SD* = 8.29) for the control group and -1.35 (*SD* = 9.10) for the exercise group; neither of these meets the MID of four T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging

from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Role Emotional T-score is below average for all participants. The below average scores indicate that these groups have greater difficulty with work and other activities due to emotional problems.

Mental Health Subscale. The Mental Health domain is based on a five-item scale. The subscale is intended to evaluate the mental health dimensions of anxiety, depression, loss of behavioral/emotional control, and psychological well-being; low scores indicate frequent feelings of nervousness or depression, while high scores indicate feelings of peace, happiness, and calmness most of the time (Maruish, 2011). For the Mental Health subscale, the control group (n = 16) had a mean pre-study score of 61.88 (*SD* = 19.31), a mean post-study score of 66.88 (*SD* = 17.30), and a mean change score of 5.00 (*SD* = 10.00). The median (range) of pre-study Mental Health scores for the control group was 62.50 (30.00 to 90.00), the post-study median (range) was 72.50 (40.00 to 90.00), and the median (range) for the change score was 0.00 (-5.00 to 35.00). For the Mental Health subscale, the exercise group (n = 18) had a mean pre-study score of 61.67 (*SD* = 17.99), a mean post-study score of 60.00 (*SD* = 19.17), and a mean change score of -1.67 (*SD* = 11.45). The median (range) of pre-study Mental Health scores for the exercise group was 60.00 (10.00 to 85.00), the post-study median (range) was 60.00 (10.00 to 90.00), and the range for the change score was 0.00 (-35.00 to 15.00).

The rank average of the control group was 20.28 as compared to the exercise group which was 15.03. There was no statistically significant difference found between the two groups ($U = 99.50$, $Z = -1.573$, $p = 0.116$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Mental Health

subscale of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, for the Mental Health subscale of the SF-36v2.

Mental Health T-Score. The Mental Health T-score is a standardized, norm-based score that transforms the Mental Health subscale, so it has a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a MID score of three T-score points, represents a clinically important difference in the participant group (Maruish, 2011).

For the Mental Health T-score, the control group (n = 16) had a mean pre-study score of 44.00 (*SD* = 10.10), a mean post-study score of 46.62 (*SD* = 9.05), and a mean change score of 2.62 (*SD* = 5.23). The median (range) of pre-study Mental Health T-scores for the control group was 44.33 (27.32 to 58.72), the post-study median (range) was 49.56 (32.56 to 58.72), and the median (range) for the change score was 0.00 (-2.62 to 18.31). The exercise group (n = 18) had a mean pre-study Mental Health T-score of 43.89 (*SD* = 9.41), a mean post-study score of 43.02 (*SD* = 10.03), and a mean change score of -0.87 (*SD* = 6.28). The median (range) of pre-study Mental Health T-score for the exercise group was 43.02 (16.86 to 56.10), the post-study median (range) was 43.02 (16.86 to 58.72), and the median (range) for the change score was 0.00 (-18.31 to 7.85).

The rank average of the control group was 20.34, as compared to the exercise group which was 14.97. There was no statistically significant difference found between the two groups

($U = 98.50$, $Z = -1.602$, $p = 0.109$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Mental Health T-score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, in the Mental Health T-scores of the SF-36v2.

The change score for the Mental Health T-score was 2.62 ($SD = 5.23$) for the control group and of -0.87 ($SD = 6.28$) for the exercise group; neither of these meets the MID of three T-score points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Mental Health T-score is below average for all participants. The below average scores indicate that these groups have more frequent feelings of nervousness or depression, as compared to the normative data.

Physical Component Summary. The Physical Component Summary score is a standardized, norm-based score that transforms the eight domain scores into a summary component score with a mean of 50 ($SD = 10$), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a MID score of two T-score points, represents a clinically important difference in the participant group

(Maruish, 2011). The Physical Component Summary score strongly correlates with the health domains of Physical Function, Role Physical, and Bodily Pain.

For the Physical Component Summary, the control group (n = 16) had a mean pre-study score of 37.19 (*SD* = 7.73), a mean post-study score of 34.82 (*SD* = 8.38), and a mean change score of -2.37 (*SD* = 5.54). The median (range) of pre-study Physical Component Summary scores for the control group was 38.04 (23.94 to 48.59), the post-study median (range) was 34.12 (19.36 to 47.36), and the median (range) for the change score was -130 (-15.46 to 10.08). The exercise group (n = 18) had a mean pre-study Physical Component Summary score of 37.70 (*SD* = 6.47), a mean post-study score of 37.08 (*SD* = 6.52), and a mean change score of -0.63 (*SD* = 4.46). The median (range) of pre-study Physical Component Summary score for the exercise group was 39.84 (27.27 to 47.95), the post-study median (range) was 38.34 (20.98 to 46.07), and the median (range) for the change score was -0.94 (-7.22 to 7.69).

The rank average of the control group was 16.38, as compared to the exercise group which was 18.50. There was no statistically significant difference found between the two groups ($U = 126.00$, $Z = -0.621$, $p = 0.534$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Physical Component Summary score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, in the Physical Component Summary scores of the SF-36v2.

The change score for the Physical Component Summary score was -2.37 (*SD* = 5.54) for the control group and of -0.63 (*SD* = 4.46) for the exercise group. The control group did have a decline in their Physical Component Summary score at the end of the study period (indicating a worsening status on the score), meeting the MID of two points. This indicates there was a

clinically significant difference in the change in the control group from pre-study and post-study; this lowering of the score indicates the control group experienced a greater impairment in their physical function at the end of the study period, as compared to the beginning. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were well below 47, indicating that the Physical Component Summary score is well below average, as compared to normative population data, for all participants. The below average scores indicate that these groups have greater limitations in physical functioning, limitations in role participation due to physical impairment, increased bodily pain, and a feeling of poor overall health.

Mental Component Summary. The Mental Component Summary score is a standardized, norm-based score that transforms the eight domains into a summary component score with a mean of 50 (*SD* = 10), based on the 2009 U.S. general population survey (Maruish, 2011). This allows better interpretation of scores; score above 50 are above average, while scores below 50 are below average. Additionally, each one-point score change represents one-tenth of a standard deviation (representing an effect size of 0.10) (Maruish, 2011). While there are variations for different diagnoses and conditions, it is generally accepted that a Minimally Important Difference (MID) score of three T-score points, represents a clinically important difference in the participant group (Maruish, 2011). The Mental Component Summary score strongly correlates with the health domains of Mental Health, Role Emotional, and Social Functioning.

For the Mental Component Summary score, the control group (n = 16) had a mean pre-study score of 42.19 (*SD* = 9.96), a mean post-study score of 45.14 (*SD* = 9.45), and a mean

change score of 2.95 (*SD* = 5.85). The median (range) of pre-study Mental Component Summary scores for the control group was 39.60 (26.07 to 57.45), the post-study median (range) was 45.95 (31.81 to 59.86), and the median (range) for the change score was 1.82 (-5.16 to 18.25). The exercise group (n = 18) had a mean pre-study Mental Component Summary score of 42.22 (*SD* = 12.09), a mean post-study score of 41.87 (*SD* = 12.24), and a mean change score of -0.35 (*SD* = 7.71). The median (range) of pre-study Mental Component Summary score for the exercise group was 43.08 (14.32 to 60.68), the post-study median (range) was 45.46 (14.32 to 58.35), and the median (range) for the change score was 0.17 (-23.09 to 14.81).

The rank average of the control group was 19.63, as compared to the exercise group which was 15.61. There was no statistically significant difference found between the two groups ($U = 110.00$, $Z = -1.173$, $p = 0.241$), indicating that the null hypothesis cannot be rejected; there is no significant difference found between the exercise and control groups for the Mental Component Summary score of the SF-36v2. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, in the Mental Component Summary scores of the SF-36v2.

The change score for the Mental Component Summary score was 2.95 (*SD* = 5.85) for the control group and of -0.35 (*SD* = 7.71) for the exercise group; neither of these meets the MID of three points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores. It is important to note that group change scores ranging from 47 to 53 T-score points are considered average (Marusih, 2011). Both the mean pre-study and post-study scores for the control group, and for the exercise group, were below 47, indicating that the Mental Component Summary score, as compared to normative population data, is below average for all participants. The below average scores indicate that these groups have more

frequent psychological distress, social and role impairment due to emotional issues, and a poor overall health.

Summary Scores for the SF-36v2. Figures 7 through 12 provide overall comparisons of the eight domains, and the component summary scores for the SF-36v2; comparisons are provided for both the 0-100 scale, and the T-score (norm-based score). On Figure 10 and 11, a horizontal line is placed at the T-score of 50.00, which is considered average. Scores falling below the three-point standard deviation (47.00) are considered below average, as compared to the 2009 U.S. population norms.

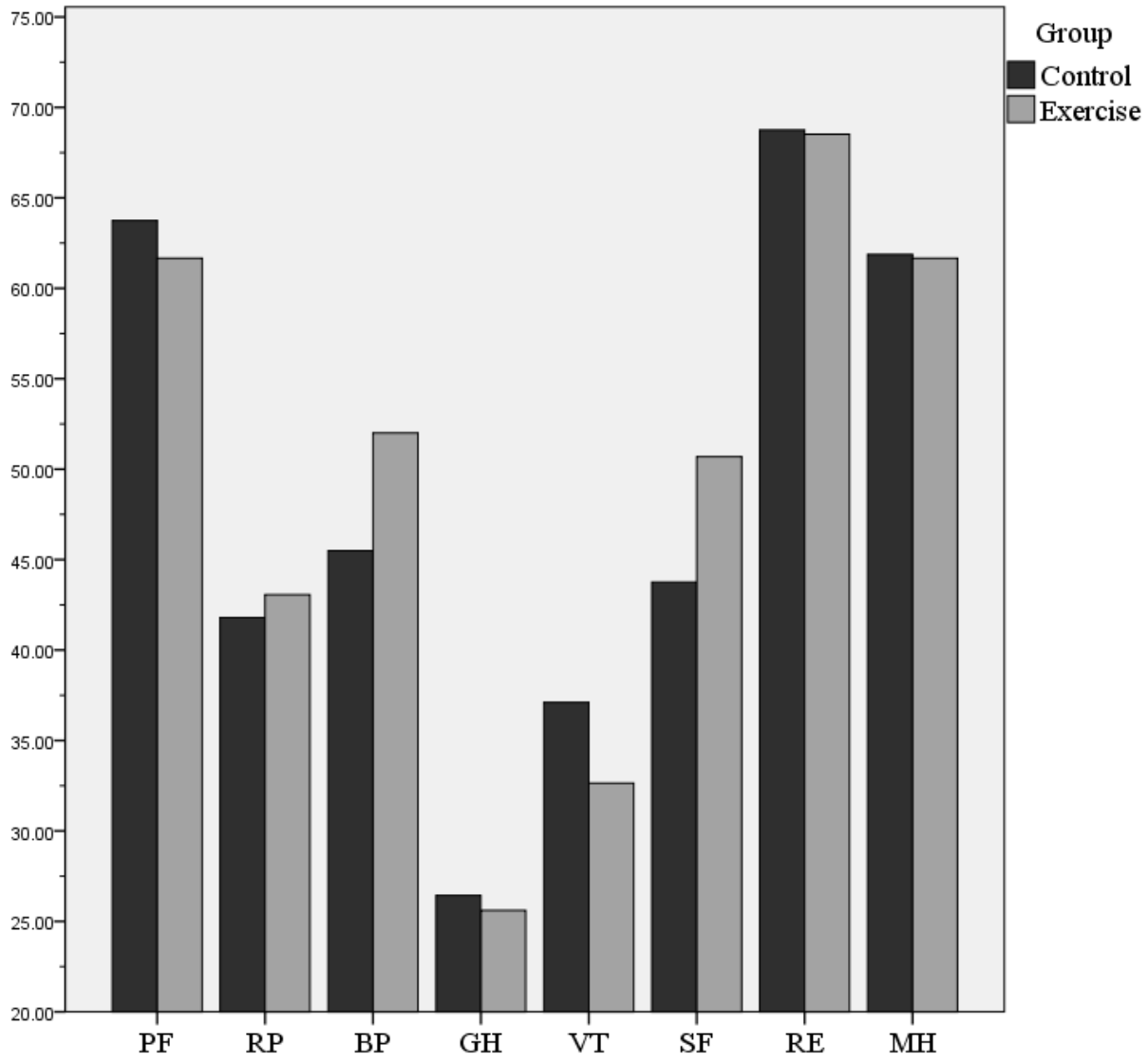


Figure 7. SF-36v2 Pre-Study Scores (Means) Based on the 0-100 Scale
Note. PF = Physical Functioning Subscale; RP = Role Physical Subscale; BP = Bodily Pain Subscale, GH = General Health Subscale; VT = Vitality Subscale; SF = Social Functioning Subscale; RE = Role Emotional Subscale; MH = Mental Health Subscale.

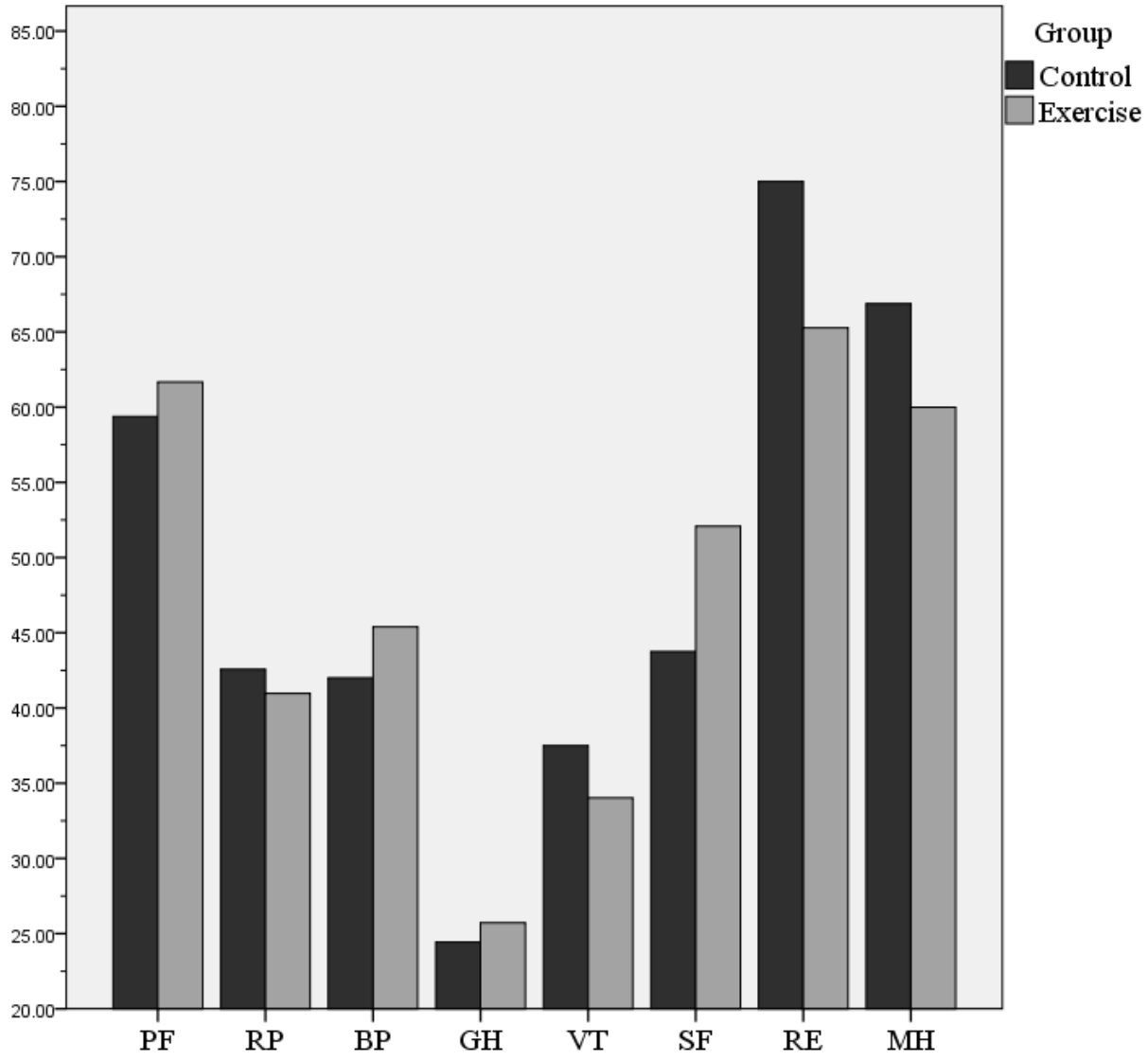


Figure 8. SF-36v2 Post-Study Scores (Means) Based on the 0-100 Scale
Note. PF = Physical Functioning Subscale; RP = Role Physical Subscale; BP = Bodily Pain Subscale, GH = General Health Subscale; VT = Vitality Subscale; SF = Social Functioning Subscale; RE = Role Emotional Subscale; MH = Mental Health Subscale.

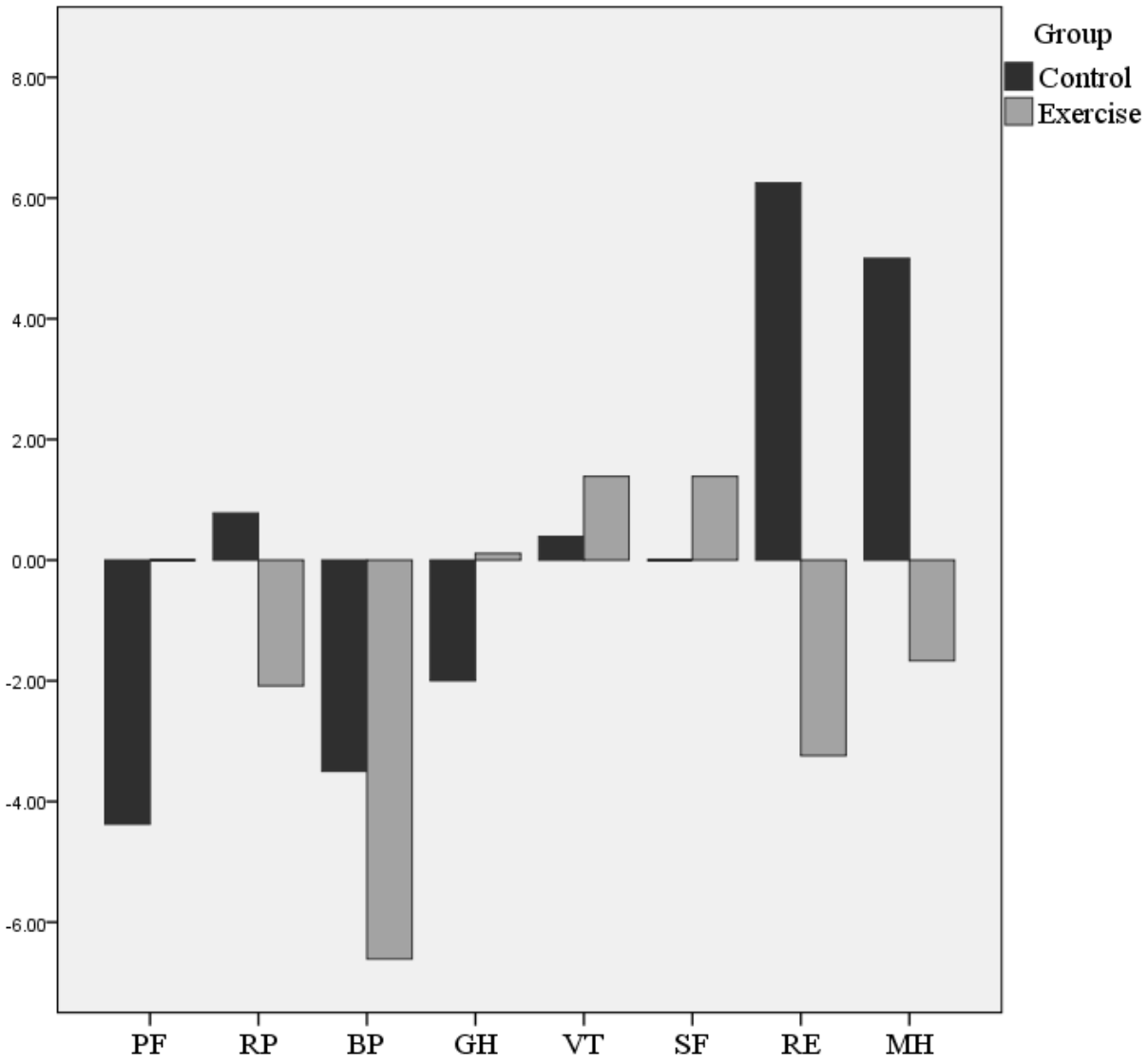


Figure 9. SF-36v2 Change Scores (Means) Based on the 0-100 Scale
Note. PF = Physical Functioning Subscale; RP = Role Physical Subscale; BP = Bodily Pain Subscale, GH = General Health Subscale; VT = Vitality Subscale; SF = Social Functioning Subscale; RE = Role Emotional Subscale; MH = Mental Health Subscale.

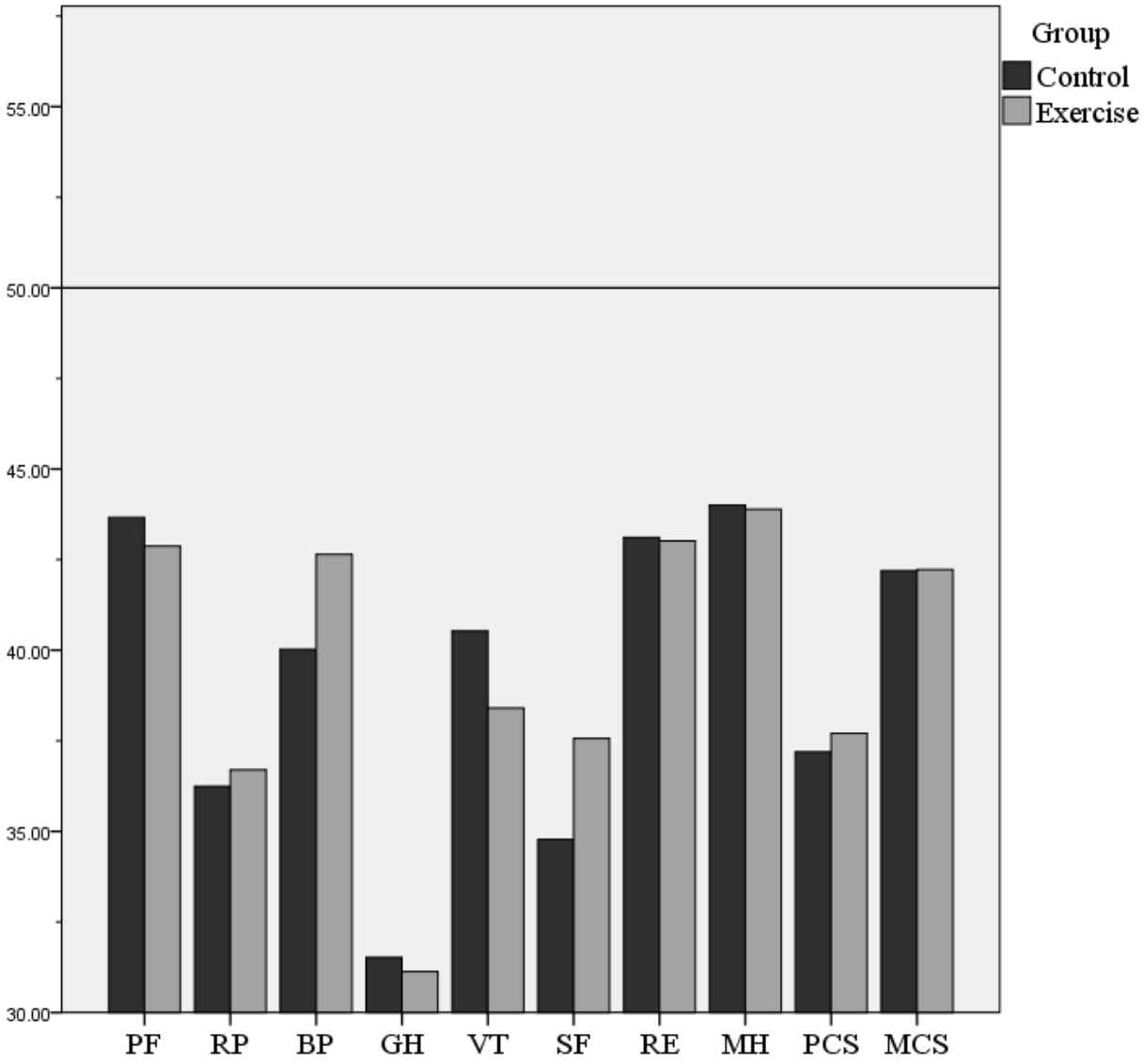


Figure 10. SF-36v2 Pre-Study T-Scores (Means)
Note. PF = Physical Functioning T-Score; RP = Role Physical T-Score; BP = Bodily Pain T-Score, GH = General Health T-Score; VT = Vitality T-Score; SF = Social Functioning T-Score; RE = Role Emotional T-Score; MH = Mental Health T-Score.

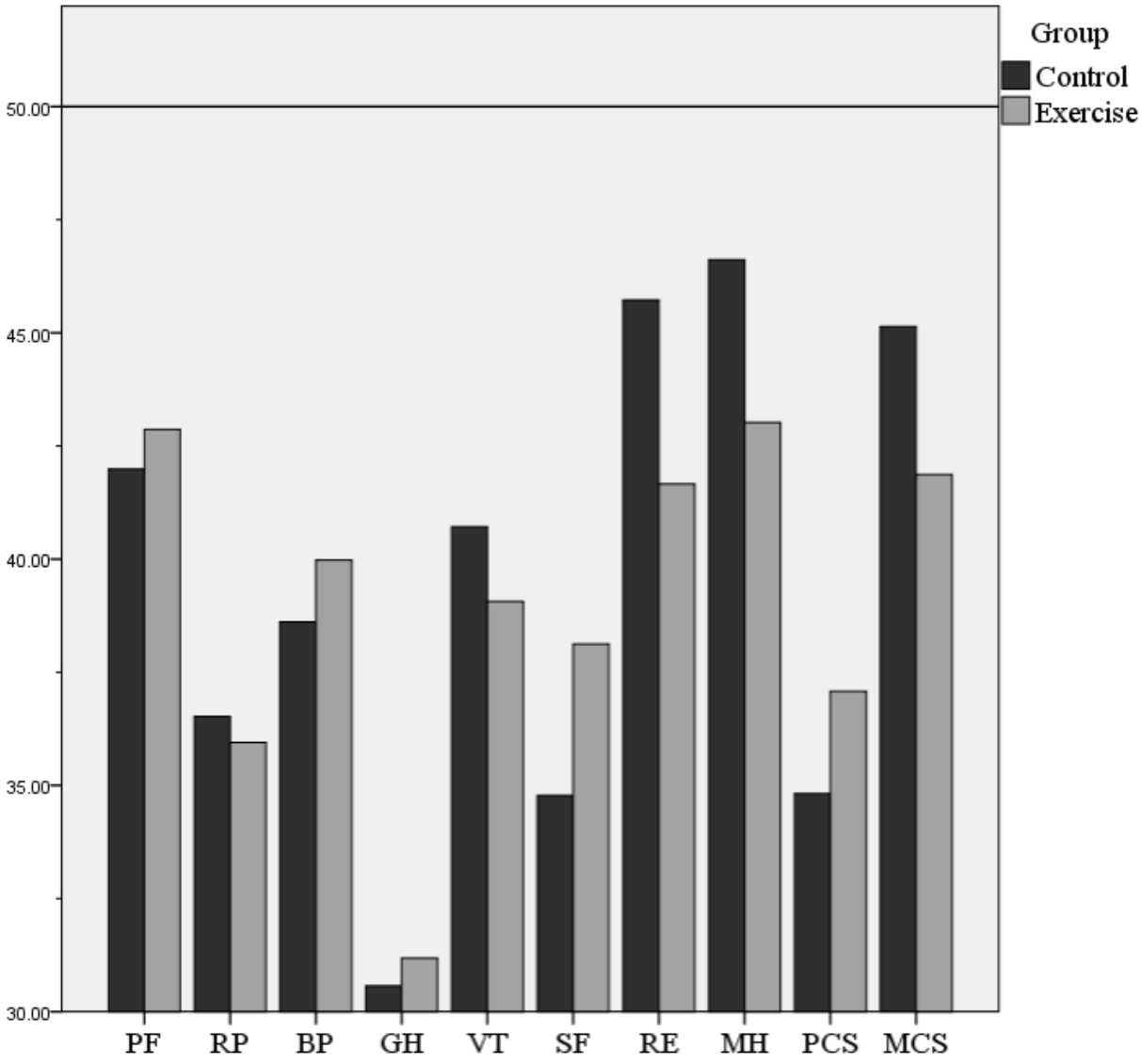


Figure 11. SF-36v2 Post-Study T-Scores (Means)
Note. PF = Physical Functioning T-Score; RP = Role Physical T-Score; BP = Bodily Pain T-Score, GH = General Health T-Score; VT = Vitality T-Score; SF = Social Functioning T-Score; RE = Role Emotional T-Score; MH = Mental Health T-Score.

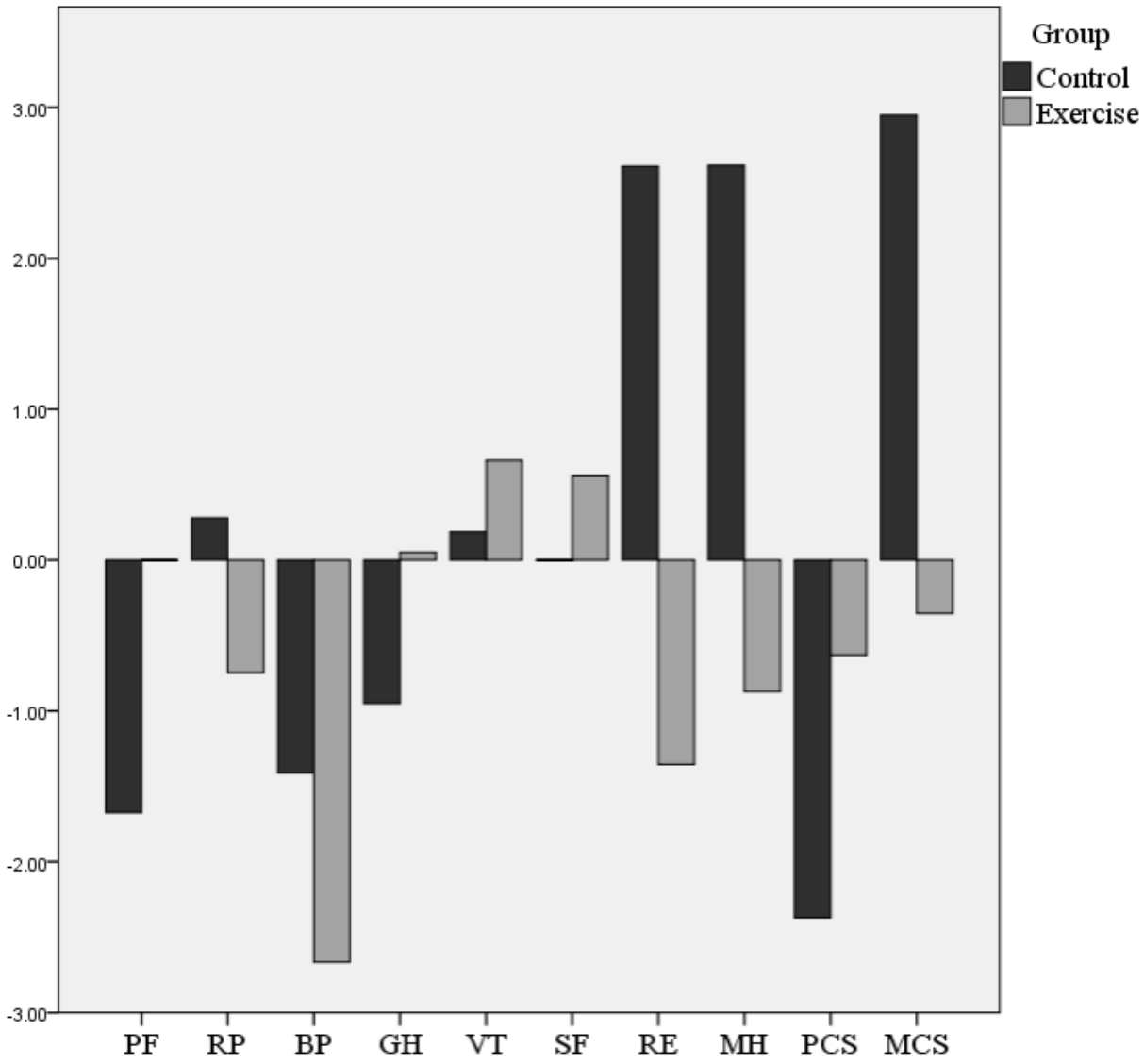


Figure 12. SF-36v2 Change T-Scores (Means)
Note. PF = Physical Functioning T-Score; RP = Role Physical T-Score; BP = Bodily Pain T-Score, GH = General Health T-Score; VT = Vitality T-Score; SF = Social Functioning T-Score; RE = Role Emotional T-Score; MH = Mental Health T-Score.

Fatigue Impact Scale (FIS).

Cognitive Subscale. The FIS Cognitive subscale is comprised of ten items scored using a Likert-type scale from zero (no problem) to four (extreme problem). The cognitive subscale evaluates how fatigue impacts aspects of cognitive function, such as concentration, memory, thinking, and organization of thoughts (Frith & Newton, 2010). Higher scores in the subscale indicate a greater fatigue impact.

For the FIS Cognitive score, the control group (n = 16) had a mean pre-study score of 17.06 (*SD* = 12.16), a mean post-study score of 15.38 (*SD* = 8.15), and a mean change score of -1.69 (*SD* = 7.75). The median (range) of pre-study FIS Cognitive scores for the control group were 14.00 (1.00 to 39.00), the post-study median (range) was 13.50 (1.00 to 30.00), and the median (range) for the change score was 0.00 (-20.00 to 7.00). The exercise group (n = 18) had a mean pre-study FIS Cognitive score of 17.17 (*SD* = 10.96), a mean post-study score of 18.44 (*SD* = 11.60), and a mean change score of 1.28 (*SD* = 6.33). The median (range) of pre-study FIS Cognitive score for the exercise group was 15.50 (0.00 to 36.00), the post-study median (range) was 21.50 (0.00 to 34.00), and the median (range) for the change score was 0.00 (-9.00 to 18.00).

The rank average of the control group was 16.53, as compared to the exercise group which was 18.36. There was no statistically significant difference found between the two groups ($U = 128.50$, $Z = -0.539$, $p = 0.590$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the scores on the FIS Cognitive subscale.

Physical Subscale. The FIS Physical subscale is comprised of ten items scored using a Likert-type scale from zero (no problem) to four (extreme problem). The physical subscale evaluates how fatigue impacts on aspects of physical function, such as motivation, effort, stamina, and coordination (Frith & Newton, 2010).

For the FIS Physical score, the control group (n = 16) had a mean pre-study score of 21.06 (*SD* = 10.79), a mean post-study score of 20.88 (*SD* = 11.08), and a mean change score of -0.19 (*SD* = 4.37). The median (range) of pre-study FIS Physical scores for the control group was 21.00 (0.00 to 36.00), the post-study median (range) was 19.50 (0.00 to 35.00), and the range for the change score was 0.00 (-10.00 to 9.00). The exercise group (n = 18) had a mean pre-study FIS Physical score of 21.44 (*SD* = 10.19), a mean post-study score of 23.78 (*SD* = 10.00), and a mean change score of 2.33 (*SD* = 4.79). The median (range) of pre-study FIS Physical score for the exercise group was 21.50 (0.00 to 36.00), the post-study median (range) was 25.50 (0.00 to 36.00), and the median (range) for the change score was 1.50 (-3.00 to 18.00).

The rank average of the control group was 14.84, as compared to the exercise group which was 19.86. There was no statistically significant difference found between the two groups ($U = 101.50$, $Z = -1.475$, $p = 0.140$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, on the FIS Physical subscale.

Social Subscale. The FIS Social subscale is comprised of twenty items scored using a Likert-type scale from zero (no problem) to four (extreme problem). The social subscale evaluates how fatigue impacts on aspects of social function, including isolation, emotions, workload, and coping (Frith & Newton, 2010).

For the FIS Social score, the control group (n = 16) had a mean pre-study score of 34.88 (*SD* = 22.46), a mean post-study score of 34.13 (*SD* = 20.72), and a mean change score of -0.75 (*SD* = 11.49). The median (range) of pre-study FIS Social scores for the control group was 26.50 (1.00 to 77.00), the post-study median (range) was 27.50 (1.00 to 67.00), and the median (range) for the change score was 0.00 (-20.00 to 27.00). The exercise group (n = 18) had a mean pre-study FIS Social score of 36.61 (*SD* = 23.00), a mean post-study score of 37.67 (*SD* = 22.88), and a mean change score of 1.06 (*SD* = 12.61). The median (range) of pre-study FIS Social score for the exercise group was 37.50 (1.00 to 72.00), the post-study median (range) was 41.50 (0.00 to 74.00), and the median (range) for the change score was 0.50 (-15.00 to 42.00).

The rank average of the control group was 16.59, as compared to the exercise group which was 18.31. There was no statistically significant difference found between the two groups ($U = 129.50$, $Z = -0.502$, $p = 0.616$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference in the scores for the exercise group, as compared to the control group, on the FIS Social subscale.

FIS Total. The total FIS score is a measure of the impact of fatigue over the past one month, with a total score value of zero to 160; a higher score is indicative of a greater degree of fatigue impacting an individual's life. A MID score for the FIS has been estimated at 10-20 points for individuals with multiple sclerosis (Rendas-Baum, Yang, Cattelin, Wallenstein, & Fisk, 2010).

For the FIS score, the control group (n = 16) had a mean pre-study score of 73.00 (*SD* = 43.63), a mean post-study score of 70.38 (*SD* = 37.78), and a mean change score of -2.63 (*SD* = 19.29). The median (range) of pre-study FIS scores for the control group was 61.50 (9.00 to 151.00), the post-study median (range) was 59.00 (2.00 to 132.00), and the median (range) for

the change score was 0.00 (-41.00 to 33.00). The exercise group (n = 18) had a mean pre-study FIS score of 75.22 (*SD* = 43.12), a mean post-study score of 79.89 (*SD* = 43.40), and a mean change score of 4.67 (*SD* = 22.12). The median (range) of pre-study FIS score for the exercise group was 70.50 (1.00 to 136.00), the post-study median (range) was 91.00 (0.00 to 143.00), and the median (range) for the change score was 0.00 (-18.00 to 78.00).

The rank average of the control group was 16.59, as compared to the exercise group which was 18.31. There was no statistically significant difference found between the two groups ($U = 129.50$, $Z = -0.501$, $p = 0.616$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the total scores on the FIS.

The change score for the FIS was -2.63 (*SD* = 19.29) for the control group and 4.67 (*SD* = 22.12) for the exercise group; neither of these meets the MID of 10-20 points. This suggests there is no clinically significant difference change between the two groups pre-study and post-study scores.

Perceived Stress Scale-10 (PSS-10). The PSS-10 is a ten-item scale with a five option Likert-type response (with zero being never, and four being very often). The scale was designed to measure of the "degree to which situations in one's life are appraised as stressful" (Cohen & Williamson, 1988, p. 33). Six of the items are negatively worded, while four are positively worded; to score the PSS-10, the positive scores are reversed, and the individual scores are added (Cohen & Williamson, 1983).

For the PSS-10 score, the control group (n = 16) had a mean pre-study score of 20.50 (*SD* = 8.54), a mean post-study score of 19.25 (*SD* = 7.22), and a mean change score of -1.25 (*SD* =

4.44). The median (range) of pre-study PSS-10 scores for the control group was 25.50 (4.00 to 30.00), the post-study median (range) was 19.00 (7.00 to 31.00), and the median (range) for the change score was 0.00 (-9.00 to 4.00). The exercise group (n = 18) had a mean pre-study PSS-10 score of 18.89 (*SD* = 8.14), a mean post-study score of 19.61 (*SD* = 9.26), and a mean change score of 0.72 (*SD* = 3.97). The median (range) of pre-study PSS-10 score for the exercise group was 19.00 (5.00 to 35.00), the post-study median (range) was 21.50 (3.00 to 35.00), and the median (range) for the change score was 0.00 (-5.00 to 11.00).

The rank average of the control group was 15.94, as compared to the exercise group which was 18.89. There was no statistically significant difference found between the two groups ($U = 119.00$, $Z = -0.867$, $p = 0.386$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the total scores on the PSS-10.

Exercise Benefits/Barriers Scale (EBBS). The EBBS is a 43-item scale with a four option Likert-type response (with one being strongly disagree, and four being strongly agree). The scale was designed to measure the perceived benefits of and barriers to exercise (Sechrist et al., 1987). Barrier items are reverse scored; the total score can range from 43-172. Higher scores indicate a greater perceived benefit, as compared to perceived barriers, for exercise (Sechrist et al., 1987).

For the EBBS score, the control group (n = 16) had a mean pre-study score of 133.81 (*SD* = 16.60), a mean post-study score of 134.13 (*SD* = 18.95), and a mean change score of 0.31 (*SD* = 9.35). The median (range) of pre-study EBBS scores for the control group was 138.00 (105.00 to 163.00), the post-study median (range) was 135.50 (103.00 to 158.00), and the median (range) for the change score was 0.00 (-19.00 to 18.00). The exercise group (n = 18) had a mean pre-

study EBBS score of 134.28 (*SD* = 12.77), a mean post-study score of 129.11 (*SD* = 12.70), and a mean change score of -5.17 (*SD* = 10.35). The median (range) of pre-study EBBS score for the exercise group was 137.00 (102.00 to 155.00), the post-study median (range) was 129.50 (108.00 to 154.00), and the median (range) for the change score was -1.50 (-31.00 to 9.00).

The rank average of the control group was 19.63, as compared to the exercise group which was 15.61. There was no statistically significant difference found between the two groups ($U = 110.00$, $Z = -1.182$, $p = 0.237$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the total scores on the EBBS.

Self-Efficacy for Exercise Scale (SEE). The SEE scale is a nine-item scale with a ten option Likert-type response (with zero being not confident, and 10 being very confident). The scale was designed to measure self-efficacy expectations relating to exercise participation (Resnick & Jenkins, 2000). The total score can range from 0-90; higher scores indicate a higher self-efficacy for exercise.

For the SEE score, the control group (n = 16) had a mean pre-study score of 53.88 (*SD* = 14.57), a mean post-study score of 51.81 (*SD* = 16.96), and a mean change score of -2.06 (*SD* = 19.86). The median (range) of pre-study SEE scores for the control group was 52.00 (31.00 to 79.00), the post-study median (range) was 53.50 (19.00 to 84.00), and the median (range) for the change score was 0.00 (-34.00 to 53.00). The exercise group (n = 18) had a mean pre-study SEE score of 53.50 (*SD* = 15.97), a mean post-study score of 46.72 (*SD* = 19.72), and a mean change score of -6.78 (*SD* = 22.27). The median (range) of pre-study SEE score for the exercise group was 56.00 (21.00 to 82.00), the post-study median (range) was 42.00 (14.00 to 90.00), and the median (range) for the change score was -5.50 (-41.00 to 54.00).

The rank average of the control group was 19.56, as compared to the exercise group which was 15.67. There was no statistically significant difference found between the two groups (U = 111.00, Z = -1.142, p = 0.254), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference in the total scores for the exercise group, as compared to the control group, on the SEE scale.

Subjective Exercise Experiences Scale (SEES). The SEES is a 12-item scale that represents a global measure of the psychological response to the experience of exercise (McAuley & Courneya, 1994). Items are scored on a Likert-type scale from one (not at all) to seven (very much so). There is no total score, instead the scale is comprised of three valuable subscales: Positive Well-Being (PWB), Psychological Distress (PD), and Fatigue. The PWB subscale corresponds to a positive aspect of psychological health. The PD subscale is inversely related to the PWB and corresponds to a negative aspect of psychological health. McAuley & Courneya (1994) found fatigue to be an important factor to consider in an individual's exercise experience, though it can be considered both positive or negative.

Positive Well-Being Subscale (PWB). For the PWB subscale, the control group (n = 16) had a mean pre-study score of 15.56 (SD = 6.11), a mean post-study score of 15.06 (SD = 5.88), and a mean change score of -0.50 (SD = 3.69). The median (range) of pre-study PWB scores for the control group was 16.00 (4.00 to 25.00), the post-study median (range) was 15.00 (6.00 to 23.00), and the median (range) for the change score was 0.00 (-10.00 to 6.00). The exercise group (n = 18) had a mean pre-study PWB score of 17.89 (SD = 5.85), a mean post-study score of 17.56 (SD = 5.33), and a mean change score of -0.33 (SD = 4.07). The median (range) of pre-study SEES PWB score for the exercise group was 18.50 (9.00 to 27.00), the post-study median

(range) was 16.50 (10.00 to 27.00), and the median (range) for the change score was 0.00 (-8.00 to 8.00).

The rank average of the control group was 16.91, as compared to the exercise group which was 18.03. There was no statistically significant difference found between the two groups ($U = 134.50$, $Z = -0.333$, $p = 0.739$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the total scores on the PWB scale.

Data was collected on the SEES PWB scale for each week during the study period. The summary data for each week can be found in Table 8. Summary change scores are provided in Table 9. A Mann-Whitney U test was performed to explore whether there was any significant difference between the control group and exercise group for the SEES PWB subscale. This analysis was conducted using the change scores, to help control for the differences in the pre-study values reported. The results for comparisons made between individual weeks are summarized in Table 10. Comparisons were also made between the pre-study change scores and each individual week. Summary information is found in Table 11. A Mann Whitney U test was performed to explore if there was any difference between the pre-study and individual week change scores; the results are summarized in Table 12.

Table 8

Summary Data for SEES PWB Subscale for Individual Weeks

Week	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study PWB	15.56 (6.11)	17.89 (5.85)	16.00 (4.00 – 25.00)	18.50 (9.00 – 27.00)
Week 1 PWB	14.88 (5.57)	16.44 (5.55)	15.00 (6.00 – 25.00)	16.00 (5.00 – 27.00)
Week 2 PWB	16.00 (5.03)	17.11 (6.54)	16.00 (8.00 – 23.00)	18.50 (6.00 – 28.00)
Week 3 PWB	15.13 (4.95)	16.00 (5.98)	15.50 (5.00 – 22.00)	16.50 (6.00 – 27.00)
Week 4 PWB	16.00 (4.34)	17.22 (6.11)	15.00 (8.00 – 23.00)	17.00 (4.00 – 27.00)
Week 5 PWB	15.63 (5.36)	16.94 (6.22)	15.50 (6.00 – 24.00)	16.50 (4.00 – 28.00)
Week 6 PWB	16.19 (6.11)	17.11 (5.89)	18.00 (4.00 – 24.00)	17.00 (5.00 – 28.00)
Week 7 PWB	15.38 (5.96)	16.56 (7.10)	17.00 (4.00 – 24.00)	16.00 (4.00 – 28.00)
Post-Study PWB	15.06 (5.88)	17.56 (5.33)	15.00 (6.00 – 23.00)	16.50 (10.00 – 27.00)

Table 9

Summary Data for SEES PWB Subscale Change Scores for Individual Weeks

PWB Change Scores	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study to Week 1 PWB	-0.69 (3.30)	-1.44 (3.84)	0.00 (-8.00 – 7.00)	-1.50 (-8.00 – 8.00)
Week 1 to Week 2 PWB	1.13 (4.67)	0.67 (5.13)	0.00 (-6.00 – 11.00)	1.00 (-10.00 – 12.00)
Week 2 to Week 3 PWB	-0.88 (2.66)	-1.11 (2.78)	0.00 (-7.00 – 4.00)	0.00 (-7.00 – 5.00)
Week 3 to Week 4 PWB	0.88 (2.12)	1.22 (3.33)	0.00 (-3.00 – 6.00)	0.00 (-3.00 – 10.00)
Week 4 to Week 5 PWB	-0.38 (3.00)	-0.28 (1.60)	0.00 (-7.00 – 5.00)	0.00 (-3.00 – 4.00
Week 5 to Week 6 PWB	0.56 (4.93)	0.17 (3.26)	0.00 (-6.00 – 13.00)	0.00 (-8.00 – 7.00)
Week 6 to Week 7 PWB	-0.81 (3.23)	-0.56 (6.16)	0.00 (-12.00 – 2.00)	0.00 (-10.00 – 18.00)
Week 7 to Post-Study PWB	-0.31 (4.38)	1.00 (6.87)	0.00 (-9.00 – 6.00)	0.00 (-13.00 – 19.00)

Table 10

Mann Whitney U Data for SEES PWB Subscale Change Score for Individual Weeks

PWB Change Scores	Rank		Test Statistics		
	Control	Exercise	*U*	*z*	*p*
Pre-Study to Week 1 PWB	18.63	16.50	126.00	-0.634	0.526
Week 1 to Week 2 PWB	17.03	17.92	136.50	-0.264	0.792
Week 2 to Week 3 PWB	18.19	16.89	133.00	-0.398	0.691
Week 3 to Week 4 PWB	17.59	17.42	142.50	-0.054	0.957
Week 4 to Week 5 PWB	18.38	16.72	130.00	-0.511	0.609
Week 5 to Week 6 PWB	16.94	18.00	135.00	-0.328	0.743
Week 6 to Week 7 PWB	18.19	16.89	133.00	-0.401	0.688
Week 7 to Post-Study PWB	17.31	17.67	141.00	-0.105	0.916

Table 11

Summary Data for SEES PWB Subscale Change Scores for Pre-Study to Individual Weeks

PWB Change Scores	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study to Week 1 PWB	-0.69 (3.30)	-1.44 (3.84)	0.00 (-8.00 – 7.00)	-1.50 (-8.00 – 8.00)
Pre-Study to Week 2 PWB	0.44 (4.43)	-0.78 (5.84)	0.00 (-6.00 – 9.00)	-1.00 (-13.00 – 13.00)
Pre-Study to Week 3 PWB	-0.44 (5.10)	-1.89 (6.52)	0.00 (-7.00 – 11.00)	-2.00 (-15.00 – 13.00)
Pre-Study to Week 4 PWB	0.44 (4.75)	-0.67 (6.05)	0.00 (-7.00 – 11.00)	0.00 (-13.00 – 13.00)
Pre-Study to Week 5 PWB	0.06 (4.60)	-0.94 (5.93)	0.00 (-7.00 – 11.00)	0.00 (-13.00 – 10.00)
Pre-Study to Week 6 PWB	0.63 (5.60)	-0.78 (5.53)	0.00 (-8.00 – 11.00)	0.00 (-11.00 – 10.00)
Pre-Study to Week 7 PWB	-0.19 (5.96)	-1.33 (8.62)	0.00 (-11.00 – 11.00)	0.00 (-18.00 – 14.00)
Pre-Study to Post-Study PWB	-0.50 (3.69)	-0.33 (4.07)	0.00 (-10.00 – 6.00)	0.00 (-8.00 – 8.00)

Table 12

Mann Whitney U Data for SEES PWB Subscale Change Score from Pre-Study Baseline

PWB Change Scores	Rank		Test Statistics		
	Control	Exercise	*U*	*z*	*p*
Pre-Study to Week 1 PWB	18.63	16.50	126.00	-0.634	0.526
Pre-Study to Week 2 PWB	18.78	16.36	123.50	-0.711	0.477
Pre-Study to Week 3 PWB	18.84	16.31	122.50	-0.746	0.456
Pre-Study to Week 4 PWB	18.19	16.89	133.00	-0.385	0.700
Pre-Study to Week 5 PWB	17.53	17.47	143.50	-0.017	0.986
Pre-Study to Week 6 PWB	18.75	16.39	124.00	-0.692	0.489
Pre-Study to Week 7 PWB	17.66	17.36	141.50	-0.087	0.931
Pre-Study to Post-Study PWB	16.91	18.03	134.50	-0.333	0.739

Psychological Distress Subscale (PD). For the PD subscale, the control group (n = 16) had a mean pre-study score of 11.56 (*SD* = 6.40), a mean post-study score of 12.38 (*SD* = 5.88), and a mean change score of 0.81 (*SD* = 5.29). The median (range) of pre-study PD scores for the control group was 11.50 (4.00 to 25.00), the post-study median (range) was 12.50 (4.00 to 24.00), and the median (range) for the change score was 0.50 (-11.00 to 12.00). The exercise group (n = 18) had a mean pre-study PD score of 9.00 (*SD* = 4.49), a mean post-study score of 9.33 (*SD* = 4.04), and a mean change score of 0.33 (*SD* = 3.14). The median (range) of pre-study SEES PD score for the exercise group was 7.50 (4.00 to 20.00), the post-study median (range) was 8.50 (4.00 to 16.00), and the median (range) for the change score was 1.00 (-7.00 to 6.00).

The rank average of the control group was 17.47, as compared to the exercise group which was 17.53. There was no statistically significant difference found between the two groups ($U = 143.50$, $Z = -0.017$, $p = 0.986$), indicating that the null hypothesis cannot be rejected. It

suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, for the total scores on the PD scale.

Data was collected on the SEES PD scale for each week during the study period. The summary data for each week can be found in Table 13. Summary change scores are provided in Table 14. A Mann-Whitney U test was performed to explore whether there was any significant difference between the control group and exercise group for the SEES PD subscale. This analysis was conducted using the change scores, to help control for the differences in the pre-study values reported. The results for comparisons made between individual weeks are summarized in Table 15. Comparisons were also made between the pre-study change scores and each individual week. Summary information is found in Table 16. A Mann Whitney U test was performed to explore if there was any difference between the pre-study and individual week change scores; the results are summarized in Table 17.

Table 13

Summary Data for SEES PD Subscale for Individual Weeks

Week	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study PD	11.56 (6.40)	9.00 (4.48)	11.50 (4.00 – 25.00)	7.50 (4.00 – 20.00)
Week 1 PD	12.44 (7.42)	9.78 (4.77)	12.00 (4.00 – 28.00)	9.50 (4.00 – 18.00)
Week 2 PD	11.81 (7.21)	10.67 (6.16)	12.00 (4.00 – 28.00)	8.00 (4.00 – 23.00)
Week 3 PD	12.56 (6.51)	11.56 (6.78)	12.00 (4.00 – 26.00)	10.50 (4.00 – 27.00)
Week 4 PD	12.19 (5.55)	9.67 (4.84)	13.50 (4.00 – 23.00)	10.00 (4.00 – 19.00)
Week 5 PD	12.06 (5.98)	10.17 (5.89)	12.50 (4.00 – 23.00)	9.00 (4.00 – 23.00)
Week 6 PD	12.50 (7.05)	9.83 (5.06)	12.50 (4.00 – 28.00)	9.50 (4.00 – 20.00)
Week 7 PD	12.31 (7.60)	11.67 (7.88)	11.50 (4.00 – 28.00)	10.50 (4.00 – 28.00)
Post-Study PD	12.38 (5.88)	9.33 (4.04)	12.50 (4.00 – 24.00)	8.50 (4.00 – 16.00)

Table 14

Summary Data for SEES PD Subscale Change Scores for Individual Weeks

PD Change Scores	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study to Week 1 PD	0.88 (3.32)	0.78 (4.71)	0.00 (-7.00 – 7.00)	0.00 (-8.00 – 11.00)
Week 1 to Week 2 PD	-0.63 (3.65)	0.89 (5.17)	0.00 (-8.00 – 6.00)	0.00 (-10.00 – 13.00)
Week 2 to Week 3 PD	0.75 (7.62)	0.89 (3.89)	0.50 (-22.00 – 12.00)	0.00 (-12.00 – 6.00)
Week 3 to Week 4 PD	-0.38 (4.42)	-1.89 (4.10)	0.00 (-8.00 – 12.00)	0.00 (-17.00 – 1.00)
Week 4 to Week 5 PD	-0.13 (2.30)	0.50 (2.09)	0.00 (-5.00 – 6.00)	0.00 (-2.00 – 7.00)
Week 5 to Week 6 PD	0.44 (4.32)	-0.33 (3.65)	0.00 (-10.00 – 10.00)	0.00 (-10.00 – 8.00)
Week 6 to Week 7 PD	-0.19 (2.48)	1.83 (6.76)	0.00 (-7.00 – 6.00)	0.00 (-14.00 – 19.00)
Week 7 to Post-Study PD	0.06 (6.52)	-2.33 (8.18)	-1.00 (-10.00 – 18.00)	0.00 (-24.00 – 9.00)

Table 15

Mann Whitney U Data for SEES PD Subscale Change Score for Individual Weeks

PD Change Scores	Rank		Test Statistics		
	Control	Exercise	*U*	*z*	*p*
Pre-Study to Week 1 PD	18.09	16.97	134.50	-0.334	0.738
Week 1 to Week 2 PD	16.44	18.44	127.00	-0.601	0.548
Week 2 to Week 3 PD	17.78	17.25	139.50	-0.160	0.873
Week 3 to Week 4 PD	18.66	16.47	125.50	-0.693	0.489
Week 4 to Week 5 PD	16.44	18.44	127.00	-0.658	0.511
Week 5 to Week 6 PD	18.13	16.94	134.00	-0.369	0.712
Week 6 to Week 7 PD	15.69	19.11	115.00	-1.121	0.262
Week 7 to Post-Study PD	17.72	17.31	140.50	-0.121	0.903

Table 16

Summary Data for SEES PD Subscale Change Scores for Pre-Study to Individual Weeks

PD Change Scores	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study to Week 1 PD	0.88 (3.32)	0.78 (4.71)	0.00 (-7.00 – 7.00)	0.00 (-8.00 – 11.00)
Pre-Study to Week 2 PD	0.25 (4.39)	1.67 (6.06)	0.00 (-9.00 – 11.00)	0.00 (-8.00 – 16.00)
Pre-Study to Week 3 PD	1.00 (6.89)	2.56 (6.85)	1.00 (-19.00 – 11.00)	0.00 (-8.00 – 22.00)
Pre-Study to Week 4 PD	0.63 (5.66)	0.67 (4.99)	1.00 (-19.00 – 6.00)	0.00 (-8.00 – 14.00)
Pre-Study to Week 5 PD	0.50 (6.11)	1.17 (4.68)	1.00 (-19.00 – 7.00)	0.50 (-8.00 – 14.00)
Pre-Study to Week 6 PD	0.94 (7.68)	0.83 (4.68)	0.50 (-19.00 – 13.00)	0.00 (-8.00 – 11.00)
Pre-Study to Week 7 PD	0.75 (7.78)	2.67 (9.39)	0.50 (-19.00 – 15.00)	0.50 (-14.00 – 23.00)
Pre-Study to Post-Study PD	0.81 (5.29)	0.33 (3.14)	0.50 (-11.00 – 12.00)	1.00 (-7.00 – 6.00)

Table 17

Mann Whitney U Data for SEES PD Subscale Change Score from Pre-Study Baseline

PD Change Scores	Rank		Test Statistics		
	Control	Exercise	*U*	*z*	*p*
Pre-Study to Week 1 PD	18.09	16.97	134.50	-0.334	0.738
Pre-Study to Week 2 PD	16.97	17.97	135.50	-0.296	0.767
Pre-Study to Week 3 PD	17.91	17.14	137.50	-0.227	0.820
Pre-Study to Week 4 PD	19.16	16.03	117.50	-0.932	0.351
Pre-Study to Week 5 PD	18.38	16.72	130.00	-0.487	0.627
Pre-Study to Week 6 PD	18.19	16.89	133.00	-0.383	0.701
Pre-Study to Week 7 PD	16.81	18.11	133.00	-0.382	0.702
Pre-Study to Post-Study PD	17.47	17.53	143.50	-0.017	0.986

Fatigue Subscale. For the Fatigue subscale, the control group (n = 16) had a mean pre-study score of 19.88 (*SD* = 5.29), a mean post-study score of 17.25 (*SD* = 6.46), and a mean change score of -2.63 (*SD* = 3.98). The median (range) of pre-study Fatigue scores for the control group was 18.50 (10.00 to 28.00), the post-study median (range) was 16.00 (7.00 to 28.00), and the median (range) for the change score was -1.50 (-11.00 to 3.00). The exercise group (n = 18) had a mean pre-study Fatigue score of 17.94 (*SD* = 7.80), a mean post-study score of 17.17 (*SD* = 7.29), and a mean change score of -0.78 (*SD* = 7.05). The median (range) of pre-study SEES Fatigue score for the exercise group was 20.00 (4.00 to 28.00), the post-study median (range) was 17.00 (4.00 to 28.00), and the median (range) for the change score was 0.50 (-21.00 to 11.00).

The rank average of the control group was 14.63, as compared to the exercise group which was 20.06. There was no statistically significant difference found between the two groups ($U = 98.50$, $Z = -1.601$, $p = 0.109$), indicating that the null hypothesis cannot be rejected. It suggests that the exercise intervention did not result in a significant difference for the exercise group, as compared to the control group, in the total scores on the Fatigue subscale.

Data was collected on the SEES Fatigue subscale for each week during the study period. The summary data for each week can be found in Table 18. Summary change scores are provided in Table 19. A Mann-Whitney U test was performed to explore whether there was any significant difference between the control group and exercise group for the SEES Fatigue subscale. This analysis was conducted using the change scores to help control for the differences in the pre-study values reported. The results for comparisons made between individual weeks are summarized in Table 20. Comparisons were also made between the pre-study change scores and each individual week. Summary information is found in Table 21. A Mann Whitney U test

was performed to explore if there was any difference between the pre-study and individual week change scores; the results are summarized in Table 22.

Table 18

Summary Data for SEES Fatigue Subscale for Individual Weeks

Week	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study Fatigue	19.88 (5.29)	17.94 (7.80)	18.50 (10.00 – 28.00)	20.00 (4.00 – 28.00)
Week 1 Fatigue	20.31 (6.50)	17.61 (7.49)	19.50 (8.00 – 28.00)	16.50 (5.00 – 28.00)
Week 2 Fatigue	17.50 (7.05)	18.33 (8.04)	16.00 (4.00 – 28.00)	20.50 (6.00 – 28.00)
Week 3 Fatigue	18.00 (6.18)	18.44 (8.50)	17.00 (7.00 – 28.00)	18.50 (5.00 – 28.00)
Week 4 Fatigue	18.13 (7.90)	16.67 (7.80)	18.50 (7.00 – 28.00)	16.50 (4.00 – 28.00)
Week 5 Fatigue	16.50 (7.83)	17.00 (7.44)	15.50 (6.00 – 28.00)	17.50 (4.00 – 27.00)
Week 6 Fatigue	18.44 (8.19)	17.39 (7.11)	16.50 (5.00 – 28.00)	17.00 (4.00 – 28.00)
Week 7 Fatigue	18.06 (8.92)	17.44 (8.96)	18.50 (5.00 – 28.00)	19.00 (4.00 – 28.00)
Post-Study Fatigue	17.25 (6.46)	17.17 (7.29)	16.00 (7.00 – 28.00)	17.00 (4.00 – 28.00)

Table 19

Summary Data for SEES Fatigue Subscale Change Scores for Individual Weeks

Fatigue Change Scores	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study to Week 1 Fatigue	0.44 (2.94)	-0.33 (6.90)	0.00 (-4.00 – 5.00)	0.50 (-23.00 – 9.00)
Week 1 to Week 2 Fatigue	-2.81 (4.26)	0.72 (4.75)	-0.50 (-12.00 – 4.00)	0.00 (-7.00 – 9.00)
Week 2 to Week 3 Fatigue	0.50 (7.58)	0.11 (3.20)	0.00 (-21.00 – 13.00)	0.00 (-7.00 – 7.00)
Week 3 to Week 4 Fatigue	0.13 (4.86)	-1.78 (5.74)	0.00 (-8.00 – 9.00)	-0.50 (-12.00 – 11.00)
Week 4 to Week 5 Fatigue	-1.63 (4.56)	0.33 (3.91)	0.00 (-12.00 – 4.00)	0.00 (-7.00 – 11.00)
Week 5 to Week 6 Fatigue	1.94 (4.22)	0.39 (3.40)	0.00 (-5.00 – 10.00)	0.00 (-7.00 – 7.00)
Week 6 to Week 7 Fatigue	-0.38 (4.53)	0.06 (7.38)	0.00 (-10.00 – 7.00)	0.00 (-20.00 – 12.00)
Week 7 to Post-Study Fatigue	-0.81 (7.72)	-0.28 (7.77)	-1.50 (-13.00 – 19.00)	0.00 (-15.00 – 20.00)

Table 20

Mann Whitney U Data for SEES Fatigue Subscale Change Score for Individual Weeks

Fatigue Change Scores	Rank		Test Statistics		
	Control	Exercise	*U*	*z*	*p*
Pre-Study to Week 1 Fatigue	16.94	18.00	135.00	-0.314	0.754
Week 1 to Week 2 Fatigue	14.25	20.39	92.00	-1.828	0.068
Week 2 to Week 3 Fatigue	18.44	16.67	129.00	-0.523	0.601
Week 3 to Week 4 Fatigue	19.66	15.58	109.50	-1.236	0.217
Week 4 to Week 5 Fatigue	16.16	18.69	122.50	-0.784	0.433
Week 5 to Week 6 Fatigue	18.94	16.22	121.00	-0.824	0.410
Week 6 to Week 7 Fatigue	17.00	17.94	136.00	-0.295	0.768
Week 7 to Post-Study Fatigue	16.50	18.39	128.00	-0.555	0.579

Table 21

Summary Data for SEES Fatigue Subscale Change Scores for Pre-Study to Individual Weeks

Fatigue Change Scores	Mean (*SD*)		Median (Range)	
	Control	Exercise	Control	Exercise
Pre-Study to Week 1 Fatigue	0.44 (2.94)	-0.33 (6.90)	0.00 (-4.00 – 5.00)	0.50 (-23.00 – 9.00)
Pre-Study to Week 2 Fatigue	-2.38 (4.36)	0.39 (6.43)	-1.00 (-12.00 – 4.00)	1.00 (-20.00 – 10.00)
Pre-Study to Week 3 Fatigue	-1.88 (6.64)	0.50 (7.16)	-1.50 (-21.00 – 9.00)	0.00 (-20.00 – 13.00)
Pre-Study to Week 4 Fatigue	-1.75 (6.60)	-1.28 (7.24)	0.00 (-21.00 – 8.00)	-1.00 (-20.00 – 12.00)
Pre-Study to Week 5 Fatigue	-3.38 (7.12)	-0.94 (7.09)	-1.50 (-21.00 – 8.00)	0.00 (-24.00 – 12.00)
Pre-Study to Week 6 Fatigue	-1.44 (7.95)	-0.56 (6.91)	-0.50 (-21.00 – 10.00)	0.50 (-24.00 – 6.00)
Pre-Study to Week 7 Fatigue	-1.81 (7.74)	-0.50 (9.78)	-1.00 (-21.00 – 10.00)	0.00 (-24.00 – 17.00)
Pre-Study to Post-Study Fatigue	-2.63 (3.98)	-0.78 (7.05)	-1.50 (-11.00 – 3.00)	0.50 (-21.00 – 11.00)

Table 22

Mann Whitney U Data for SEES Fatigue Subscale Change Score from Pre-Study Baseline

Fatigue Change Scores	Rank		Test Statistics		
	Control	Exercise	*U*	*Z*	*p*
Pre-Study to Week 1 Fatigue	16.94	18.00	135.00	-0.314	0.754
Pre-Study to Week 2 Fatigue	14.00	20.61	88.00	-1.948	0.051
Pre-Study to Week 3 Fatigue	15.06	19.67	105.00	-1.352	0.176
Pre-Study to Week 4 Fatigue	17.88	17.17	138.00	-0.208	0.835
Pre-Study to Week 5 Fatigue	15.38	19.39	110.00	-1.180	0.238
Pre-Study to Week 6 Fatigue	16.44	18.44	127.00	-0.590	0.555
Pre-Study to Week 7 Fatigue	16.34	18.53	125.50	-0.642	0.521
Pre-Study to Post-Study Fatigue	14.63	20.06	98.00	-1.601	0.109

Qualitative Data Analysis

The phenomenological qualitative portion of the study explores how participants perceive stress, fatigue, and QoL, as well as their perceptions about participation in a low to moderate intensity exercise program. Data was collected from post-study interviews with participants who underwent an eight-week exercise program, as well as from those who were allocated to the control group. Data was collected through semi-structured interviews (Appendix F) and from journal entries provided by the participants, from both the exercise intervention group and the control group, during the eight-week study period (triangulation via multiple sources). Participants were provided with copies of their interview transcriptions to clarify, edit, or further explain their responses (member checks for further triangulation of data). The interview transcriptions and journal entries were coded by the primary researcher using the NVIVO, version 11 software (QSR International Pty Ltd, 2015). The transcriptions and journal entries

were also examined by two external reviewers, including a physical therapist with expertise in the areas of stress and quality of life and a physical therapist educator with mixed methods expertise. Research bias was minimized by external reviewers without any prior interactions with this patient population. The themes generated by the qualitative narrative data were confirmed by the external reviewers.

Qualitative Research Question: What is the lived experience of participants diagnosed with PID as it relates to stress, fatigue, QoL, and exercise?

Qualitative Research Themes

Based on the exploration and analysis of the interview transcriptions and eight-week journals for the participants in this research study, four key themes emerged. The first of the four key themes expressed the participants' need to redefine a 'new normal', the struggle over the loss of their identity, recognition of personal limitations, and their adaptation to lifestyle changes. This theme centered on the concepts of identity and self, and the adaptations that occurred pursuant to their chronic disease.

The second theme addressed the concept of living with a chronic disease; this theme explored the physical and emotional challenges of living with a diagnosis of PID. This included perspectives about the social isolation they experienced, the overwhelming feeling of fatigue, the impact of chronic disease on emotional well-being, the impact of chronic disease on QoL and activities, and concerns about the experience of brain fog. Participants explained the feeling of brain fog as a cognitive impairment that included forgetfulness, word finding deficits, and processing issues.

The third main theme is about facing the stigma associated with an invisible, chronic disease, such as PID, exemplified by the participants' frustration when people say, "you don't look sick." Participants explained that their chronic disease is often not visible, and they may not look acutely ill. When they were forced to cancel plans or go to another medical appointment, friends and family often questioned whether they truly had a serious medical condition. Participants also expressed frustration that their friends and family did not understand the gravity of their chronic disease, because the condition is often invisible to others.

The fourth theme that emerged was that exercise is exhausting, and the participants "wanted to exercise, but (were) just too exhausted." Nearly all participants expressed interest in wanting to exercise and a perception that exercise had overall health benefits. However, they also expressed they were often too fatigued to consistently participate in an exercise program, and that exercise added to that fatigue. They also described frustration in not being able to exercise as vigorously or consistently as they would like to (or had done in the past). Finally, they described how having limitations in their ability to participate in exercise contributed to frustration and depression; their inability to exercise consistently reminded them of their physical limitations, which contributed to greater emotional distress.

Pseudonyms, which are not related to the names of any of the participants in the study, are utilized to share the information from the interviews and journals.

Theme One: Redefining a new normal: "Not the person I used to be." This theme explored the concepts of redefining a 'new normal', the loss of identity ("who am I") and recognizing personal limitations and adapting to an altered lifestyle. The participants in this study conveyed a sense of emotional frustration, anxiety, and despondence due to alterations they experienced in their sense of self. These alterations were directly connected to their PID

and its associated medical issues. They found themselves having to accept the reality of a chronic disease, causing many to mourn the loss of their former self.

Redefining a 'new normal'. PID is not a curable or transient condition. As a chronic disease, PID has a life-long impact on the individual, both physically and emotionally. Many participants discussed the difficulty they had, in both adapting to their 'new normal', and in trying not to let the disease define who they are and how they live. Melanie mentioned in her interview:

> *It impacts the most I would say, physically and emotionally. You are torn between trying to act like a regular human being, get out there, do your thing…I want to go to work, I want to be able to participate in stuff that my kids want to participate in, like go hiking or whatever. So, it is hard, because you've got to find that balance between doing it, and overdoing it, because if you overdo it, then you are in trouble. If you feel like you are not doing enough, it kind of impacts the emotional side too, because then you really do feel down on yourself. You feel like you are not doing enough, if that makes sense.*

She expressed her desire to act like a "regular human being," implying she does not always see her life as 'normal'. Her desire to participate in life and her fear of overdoing it made her fatigue and illness worse, which underlies her need to alter her lifestyle and adapt her behavior.

Some participants described the strategies used to combat the challenge of maintaining as normal a lifestyle as possible. Christopher noted:

> *I really try hard not to let it impact my life. It does make things a little bit harder, just feeling motivated at work, feeling motivated to do various things at home. But, I always just try to push past just as much as I can. I'm just basically trying to live my life if I had otherwise. It's always kind of been my goal not to let the PID impact me at work or impact any activities with my family, with my kids. So, I really just try to push past whatever fatigue that I'm feeling, or any mental or emotional resistance that I'm feeling towards doing something and just try to be as seamless as possible during that time. I am a member of multiple Facebook groups about PID and I go days without looking at any of those, because sometimes I feel like there are people who would just dwell way too much on it and I don't want to do that. I want to try to just move forward with my life as if I don't have this diagnosis, I need to move ahead.*

Christopher further expanded on this, adding:

> *I just try to move ahead with it. My son has some mild PID issues, not to the degree that I have at this point, but I think that might come in the future. I try to just set the best example for him so that if the time comes that he has a full-blown PID, which needs infusions, or whatever the case is, that hopefully he can see at that point, hey, you can live a normal life with this.*

While Christopher presented an optimistic outlook on his life and strived to be a role model for his son, he still admitted there was an impact on his lifestyle and activities. He recognized the impact of his PID but strives to live as normal a life as possible. Likewise, Donna expressed satisfaction in having an almost normal life:

> *It could be better, but I have almost a normal life. I work full-time, I used to work two jobs, I needed to leave one because the work was too much for me. But, I have IVIG every three weeks and I try to keep a normal life. By the end of the third week, I am extremely tired, and I need to slow down. All in all, I'm satisfied, and I decided that my Primary Immunodeficiency is not going to run my life. I try to keep a positive attitude with all these things I'm going through. I get anxious and sometimes I feel like I want to give up, but I keep fighting. I'm on therapy, on and off, for a long time. I am a therapist myself, and I'm in psychotherapy on and off, and sometimes because I don't vent it out, about my disease about how tired I am…in therapy I do it*.

Loss of Identity: "Who am I?" Some of the participants recognized that the lifestyle adaptations and their 'new normal' have had a significant emotional impact on them. Connie described the loss of her old life, the loss of her identity: "*The emotional, mental, part of it is that I've had to accept the fact, and grieve, that I'm not the person that I used to be. It was really a hard step to take to accept that and learn to live with it*." The concept of grieving the loss of your former self is profound and recognizes the depth of the emotional impact of a PID diagnosis. Many of the participants struggled with this perceived alteration in their identity, due to their chronic medical disease. A similar depth of emotion was evident in the interview with Cynthia:

> *I feel like I just want to live a "normal life," like everybody else. I feel like I have a very poor quality of life right now. So, today, I feel super happy because I feel almost normal, but I'm also apprehensive because I know it can change at any time and my infusion is coming up. I'm going to start getting sick again in a couple of days away. So, I'm very apprehensive.*

Individuals with a diagnosis of PID often refer to themselves as zebras, to represent the rarity of their medical diagnosis. In medical school, doctors learn the saying, "when you hear hoof beats, think horses, not zebras" to teach them to look for the most common possible diagnosis, not the unusual ones; PID may present with common symptoms, but is not a common diagnosis (IDF, 2018). Cynthia further discussed the loss of her identity as a nurse, and her resistance to assuming the role of the patient, in her journal entry:

> *I hated the idea of being a patient long before ever becoming a zebra. I remember working as a nurse in the hospital caring for chronically ill patients thinking how awful it must be to constantly be at the doctors or in the hospital and how I would hate that. I remember like it was yesterday, and it was years ago*.

Cynthia expressed how moments of being normal, with a diagnosis of a chronic disease, can be fleeting. She conveyed her fear and apprehension that the moment of normalcy is temporary; these individuals are always waiting for the disease to strike again, physically and emotionally. Melanie expressed joy for a day of feeling 'normal' in her journal:

> *Feeling much better today! I went for a walk with the kids at a local Rail Trail. It felt so amazing to get out of the house and get some fresh air and exercise! I always feel better when I get fresh air. The stress of having a chronic illness goes away and I feel like a normal person. I know I'll be tired tonight and tomorrow (I always "pay for it" if I push too hard) but it feels amazing to be human for a little while*.

Melanie also reinforced the idea that normal is a fleeting concept, yet it is a concept that is strongly sought out by this population. She raised concerns for "overdoing it" with her activities, and the apprehension that she will be punished (through increased fatigue or illness) for acting

normally for a time. Melanie explained her perceived loss of normalcy in her journal entry, acknowledging a loss of self, similar to the grief expressed by Connie:

> *Overall, I think my quality of life is pretty good. I can't complain...but there are definitely days that I need to. I'm sure that I'm not alone in regard to feeling like a burden, useless...trapped in a body that feels like it doesn't like you. I feel terrible that I can't be the mom/wife/daughter/sister/aunt, etc. that I used to be...I can only do the best I can to be the best mom/wife (etc.) I can be now.*

Melanie expands on this theme in her other journal entries, as she recognized that the chronic disease did not impact just her, but also her family:

> *Everyone is home from work and we went for a hike! This time we went to a National Wildlife place near our home. It was so fun! I am tired but super happy that we did it! Today, I actually felt like my normal self...like I used to feel like. My daughter actually said that she was happy today because I looked happy. It is kind of sad to hear your children say things like that. It hits home that you haven't quite been like yourself...I hate CVID in those moments. I love being there for my family...CVID takes me away from them. Not in the literal sense, but I can't do everything I want to do...just be a normal mom*.

The emotional depth of her statement is impactful; what is so effortless for many, to just be a "normal mom," she expressed as a unique experience for her. She relayed how her chronic disease appears to have stolen that feeling of normalcy from her; changing how she previously identified herself.

Participants relayed the emotional impact of recognizing what they perceived as a 'new normal', along with a loss of their previous identity. Lori simply stated, "*Really missing my old self."* The struggle to find a balance emotionally and physically within this perceived 'new identity' was captured in Donna's journal entry, *"I was offered a very interesting position at UCLA, working in HIV/AIDS clinic, my area of expertise. I rejected, the intense schedule was too much for me. My job is totally flexible, even though I did the right thing, I felt very anxious.*" Making this decision was clearly difficult; it emphasizes how she saw herself now, in having to

make a job decision based on her current personal limitations. The emotional distress this caused was evident in her journal entry.

Marsha also struggled with similar emotions: frustration over her diminished QoL, an inability to keep up with daily tasks, and a loss of her identity:

> *I was going to say that it sucks, but that makes me sound ungrateful that I am still alive and able to function at a minimal level. I wish the quality were better. Some of my colleagues' debate quality vs quantity. I am not yet at that point, although I fully understand their points. I continue to hope for both quality and quantity. This is so "not me."*

She also journaled, *"fatigue seems to trump joy as a general rule,"* and *"I miss going to church and I don't like the isolation that CVID has brought into my life*."

Good days and bad days were a concept many of the participants spoke about. Bad days often followed good days, typically because they would take advantage of feeling good and would do too much. Courtney, diagnosed more recently, tried to explain her resistance to accepting this 'new normal':

> *I'm definitely much more positive and hopeful on the good days. The bad days, such as a really bad day, or if I've had several in a row, I can get pretty down and depressed, because it takes a toll. I was a competitive athlete as recently as like three years ago. To go from that to trying to get the mail, as a good day, it is hard mentally to wrap my mind around. I should adjust to a new normal. I still haven't accepted that this is going to be the way it is going to be forever. I'm hoping this is just a challenging time right now. I still hope that I will be able to get back to competing and doing what I love. So, I do get depressed. The yoga helps, and just trying to keep a positive attitude helps, and also accepting, I think acceptance of this is what life is like right now. This is how I have to kind of budget my energy…accepting my limitations right now.*

As much as she tried to resist the idea of a 'new normal', Courtney admitted to accepting her current limitations to avoid overdoing her activities.

Good days and bad days were also described by Amanda:

> *Just like before, there are good days and bad days. There are days that, on my really good days, I am high on life and happy and feeling great, enjoying my life. And then there are really rough times that I'm overwhelmed, and I get very frustrated and just upset that I just don't feel like my body can do what my brain wants it to do. And I have all these goals and ambitions and I want to be able to do all this stuff and I just can't physically get done and it's very upsetting. I've cried a lot of tears and it didn't really do any good, but I struggle sometimes dealing with that. It's definitely not an easy thing to try to deal with, and I wish there was more support out there for people like me that are trying hard to stay in the workforce. Because it seems like most people end up on disability or retired or whatever, but some of us are young and want to continue in our career. I really enjoy what I do, and I want to continue, but I just feel like it fights against me. It is so hard to try to continue on being a functioning member of society when you feel like this. I really don't go out much and I don't make commitments that far in advance because, quite frankly, I don't know if I'll be able to keep them. And I'm so tired of having to break commitments that I just don't make them. I just don't get involved as much, because I don't feel like I can. I know that if I feel like it, I can do it, but other people aren't as understanding.*

Amanda mentioned the struggle to continue to contribute to society, to achieve personal goals, and the social isolation she feels, due to her disease.

These individuals, almost universally, explain how their experiences can be frustrating and overwhelming, often leading to issues with their emotional well-being. Cynthia expressed the frustration she felt in a journal entry: "*My weight continues to drop, I almost ended up in the ER last night and again this morning, instead, my bathroom floor. These are tough times that require patience and I am learning to be patient. I am a nurse, not a patient. I guess lately I have no choice."* Her frustration was evident as she struggled to retain her identity as a nurse, rather than that of a patient. Her journal expresses the depth of her despondence, as she struggles to hold on to how she saw herself, before her diagnosis of PID.

Many of the participants expressed concern in recognizing they are not the same person they were before. They frequently questioned who they were, their identity, and how it was linked to their chronic disease diagnosis. For some, the diagnosis of PID became central to their

identity, while others fought to not be defined by their disease. This caused frustration and disappointment for some, especially if they saw themselves as not achieving their goals or living life to the fullest. Lori shared that she saw improvement in her QoL due to her treatment, though recognizing she has changed:

> *My current quality of life, I would say is pretty good, finally, after a few months of being on treatment for the immune system deficiency, I'm finally responding and feeling a lot better. Trying not to compare how I used to be, as to the how I am now. Part of that is with the diagnosis, part of that is I'm getting older, which everyone in the medical field likes to tell me, though I don't like that. But I would say overall for my age and what my body has been through, I'm doing pretty good. I don't have a problem with the diagnosis, it is what it is. My treatment is working, so my numbers are good and as long as I can just continue with the treatment, I'm okay with that. I don't like that it has made me a little bit more germophobic than I used to be, but I figured the longer I'm on the treatment, the better my body will be able (to) respond and not get sick with the least little things.*

Susan, who has been on treatments for a much longer time, had similar feelings, though she was less satisfied that her diminished QoL had altered her ability to perform her normal activities: "*I would say mediocre. It's not how I saw myself if this was 15 years ago. I wouldn't be predicting that I would be…dysfunctional is not a good word, but less than optimal most of the time. I'm not able to do things that I used to be able to do, and I'm sick a lot.*"

Maureen spoke about the changes she saw in her ability to accomplish even the smallest of tasks. She felt she was functioning at a much lower level, compared to when she worked full-time as an advisor at a university:

> *I used to be a university advisor and I had a reputation for not making mistakes on degree plans or graduation audits. I had a reputation for solving a lot of problems for students with solutions that other people couldn't think of…more creative solutions and I can't even do paper work now*.

The change in identity can have a profound emotional impact on people. Angela expressed distress over her inability to make decisions, something that would have never been an issue

when she worked as a vice president for marketing and sales in a large company. She also spoke about grieving the loss of her prior lifestyle and identity:

> *Whereas before, I was the vice president in a sales and marketing for an international firm and I had to make decisions all the time. I find it very difficult to make decisions when I'm stressed. I decided to become an activist recently and I set up my own Facebook group for the people diagnosed late in age. That put a different spin on things for me and I use my sales and marketing skills to advance my objectives. That's kept me busy and has kept me positive, but I still do get sad about how much my life has changed, and how I depend on others…I think we all should have some sort of counseling because, I'm pretty sure my depression for a year was mourning the loss of my lifestyle….I was a very inpatient person, everybody had to keep up with me, if they didn't, they were out. Now, I can't keep up with anybody, so I've just become more patient.*

The interviews and journal entries expressed a variety of viewpoints and emotions experienced by the participants in this study. Recognition of the difference between their past life and identity, and their current life and identity shows the challenges faced as these participants struggle to adapt to their 'new normal'; their loss of identity was further complicated by the lifestyle adaptations they had to make to accommodate the limitations imposed by their diagnosis and its associated symptoms.

Recognizing personal limitations and adapting to an altered lifestyle. Redefining a 'new normal' and adapting to lifestyle changes was apparent in how participants recognized the limitations imposed upon them by their disease. For many of these participants, having to change their expectations and recognize they must adapt to living with a chronic disease had a profound impact, not only on them, but on how they perceived their relationships with others. For many, it was a recognition that they were not able to do what they consider to be 'normal' things that they were once able to accomplish, or, if they do those activities, they must pay a price.

Kimberly noted the impact of the disease on her life and how those around her did not understand her struggle, "*I think I only have three friends that really get it, and nobody else does. They have no idea because I push myself all the time. Trying to keep up and do, until I crash*." That need to find balance within their life, and the guilt that goes along with finding that balance by taking time to rest and recharge, was expressed by Melanie:

> *I feel bad because I feel like it affects not only me, but the people around me, that live with me. Who I feel I should be there for and I feel like almost by taking that half hour just to shut off for a while, that I almost feel guilty that I am not with them. But they understand and I'm really glad they do understand that I need that some days more than other days.*

Melanie also recognized the need to adapt her lifestyle by trying to stay active, yet being cautious not to overexert herself, "*I love exercise but it's just finding that balance I guess between, wanting to push ourselves and then pushing yourself too far and regretting it after the fact. Yeah, I just like to try to stay as active as I possibly can, I guess*."

Tara also expressed her concerns about not being understood by friends and family:

> *So many of us write and say, my family doesn't understand, my friends don't understand. Having people in your world, where you have people that actually understand and can support, just the reality of all what it all is. Then I can't tell you that I can really understand any of it, which then fades into a, "am I going to be sick for the rest of my life?" That emotional knowledge, that psychological knowledge that, at a genetic level, it doesn't seem like there is any hope for ever, ever fixing what is broken. That would be an area to look at in terms of the acceptance, because if we are not embracing and accepting the reality of whatever this is, that causes more illness, ultimately. You cannot find a community inside of any other community except our community. You can't talk to your husband, you can't talk to your daughter, they are never really going to get it*.

By acknowledging there is no hope for ever fixing what is wrong with her immune system, Tara projects the emotional strain she endures. While there may be a treatment, there will always be the disease, ready and waiting, something she feels even her family cannot comprehend.

The participants in this study expressed their struggle in redefining their identity. They recognized changes within themselves, linked to their chronic medical condition. Some participants mourned the loss of their former self; they struggled to accept this 'new normal'. Others fought to ensure that their PID did not define who they were, but did acknowledge that they had made adaptations to how they had previously lived their lives to accommodate certain aspects of their disease. Most participants noted alterations in their lifestyle due to their PID, though the degree of alteration was highly variable.

Theme Two: Living with the challenge of a chronic disease…"It's hard putting on a healthy show. I want my life back!" The participants in this study described many challenges related to living with a chronic disease. These challenges include the concepts of social isolation, overwhelming fatigue, the impact of chronic disease on emotional well-being, the impact of chronic disease on QoL and activities, and brain fog. Many participants described their attempts to act healthy for the benefit of others, only to collapse at home later. Some participants relayed that acting healthy (or 'normal') often caused them to "pay a price" later; this price was typically through fatigue, emotional distress, or social isolation.

Social isolation. Some participants experienced a greater degree of lifestyle alteration and social isolation than others due to their PID. During her interview, Claire expressed:

> *I do cry out of frustration, there was a lot of times where I have things planned and then I have a paper due and I just can't deal with it. So, I had go out and re-create myself and be more social. I don't have a social circle as it is. So, I kind of just, kind of not go out and make plans and then I just cancel. Then I am scared to fly, because I don't want to get germs. Then I don't want to be some place where they don't have good medical care, because I want to be at home when I'm sick. So, it paralyzed me from, in a lot of ways, in living my life*.

In describing how she felt paralyzed by the disease, Claire clearly explained the extent to which lifestyle alterations can limit living life for some individuals diagnosed with PID.

Having to alter activity levels to avoid illness that results in social isolation was also presented by Tina:

> *But there is no magic supplement, there is no magic as seen on TV product that's going to help with any of it. Part of its life and part of it is just what I have to do for me. Now if I feel like I've hit my low, I'm going to stop. I'm not going to keep pushing, because I know that what may look just like me being lazy to one person, to me, it means I might avoid pushing myself to the level of getting sick. Again, living in a region with low health care options, actually brings about low awareness of themselves. So, the number of people who don't think about, "Hey, I've got this barking cough but I'm just going to go stand next to you anyhow." Or the number of people who, well, "it's just viral, it's not a big deal." Well, you know, it can be a big deal, it just may not be to you. So, I will avoid certain situations if there is going to be somebody going along with, who I know is currently sick or any of that. And at the same time, because I don't want to be exposed, if myself and my kids do have something we will avoid going somewhere to avoid exposing others*.

Tina's recognition that there is no magic supplement to fix her disease, or easy way to adapt her lifestyle is a powerful insight into how difficult it is for Tina to accept the permanence of her disease.

The concepts of social isolation and alteration of lifestyle are similarly evident in the interview with Rebecca, who explains:

> *When you're tired it's hard to get things done and you get that compounding effect. I like things to be a certain way in my house then, sometimes at the end of the day, I'm too tired to collect laundry and go down to the basement and do a load of laundry. So, then the weekends are spent doing a lot of errands and household chores, because I was too tired to do that during the week. And then, it's like those household chores have now interfered with social experiences. Or, other things and even if I'm tired all the time, you are making a lot of calculations and decisions of where you're going to spend your energy. So, my friend's bachelorette party will be sometime in the next two months and I will have to make a decision based on, do have a time to be in the hospital or be sick and go to the bachelorette party…over the years I go less and less places…I try not to go to the store if it's Christmas when it's flu season. So, I feel like if I didn't have the issue I would*

> *be able to be more social and more interactive, but since I do, and I'm trying to prevent being sick, I have to isolate more than I would like to.*

Social isolation was also an implied concern mentioned in the interview with Michelle: "*I would go to work, you know, work 40, 60 hours, some weeks, come home, sleep, go to work. On weekends, I was starting to lose friends and relationships, because it completely consumed me and then I had no life."*

Marsha explained the change in her QoL and how her PID impacted her socially, contributing to her isolation. Despite her personal experience as a medical professional, prior to her diagnosis, she admitted she did not realize the impact a rare, chronic disease could have on a person's life, until she had to face it herself:

> *My current quality of life is…I pretty much stay at home. It's not anything like pre-CVID quality of life when I was out and working and doing sociable things. But it's kind of the new quality of life. I have grandchildren that come over and they keep me entertained and busy, but for short periods. I don't go out in crowds, don't go to church anymore. That used to be a big part of my life. They're always looking for volunteers at my grandkids' school. I would love to do that, but I can't. I have a PhD in nursing, so I should have known what CVID was. I certainly understood immune deficiency, but never really realized what CVID was and what it did to peoples' lives. I never had a patient with it in all my years of nursing.*

Social isolation was mentioned by several participants as having an emotional impact on their ability to live with their chronic disease. Claire commented, "*I think it's what, probably what everybody else says, is how isolating it is and you know, you don't realize how much challenges that you have from having it.*" Kimberly profoundly explained:

> *I was so happy they found something that made sense. I was happy. Then I was angry. "Why did it take so long to get diagnosed?" CVID is lonely and depressing. Friends don't want to hear about me being sick all the time. I have to cancel plans, all the time. I have not been able to use my gym membership.*

The journals of the participants confirmed their feelings of social isolation and the effects of pushing too much, that result in necessary lifestyle adaptations. One of the journal entries from Tina expressed:

> *Two or three days ago I pushed myself. I did more than usual and pushed through every request my body made to stop. We had to get the house clean. I'm paying severely now. I feel tired and exhausted to levels that no caffeine will touch. I just want to pass out, but have too many responsibilities to stay in bed for an entire day, never mind that laying for too long actually makes me hurt worse. I don't think that there's a muscle in my body that doesn't hurt, they feel weak as well. My joints feel like I've been hit on each one. But just the idea of moving that much or standing that long is making me hurt that much more. How am I ever supposed to lose weight or get even an ounce healthier if just deep cleaning my house can lay me up for days? I can't even begin to think about doing more exercise than that, it hurts to think about it.*

Tina's journal entry described the punishment, courtesy of her body, for trying to do things 'normal' people are generally able to do. The physical and emotional impact of her chronic disease on her lifestyle were evident. Tina continued to journal about her need to rest from her routine. She questioned whether her body would adapt if she continued to push, or whether it would just shut down:

> *Well, my stress levels haven't changed, not that I expected them to at this point. I'm more worn down and drained now than before, I think, but now it is the exhausted level of just dragging really hard versus the fresh-stress fatigue that happens right away. Like today, I ended up on my feet for too long and now I hurt so bad that I could collapse. I do wonder if it would change if I pushed through and repeated days like this every day and if I would adjust and get used to it or if my body really would shut down, like it feels it would. I'm praying that the rest of this week is calmer than last week so that my stress levels can go down.*

While the physical and emotional impact of a chronic disease can prove to be challenging, there is an additional layer of impact resulting from the treatment of the disease. Monthly, weekly, or daily infusions, often with significant side-effects or time requirements, as explained by the participants, can add to the emotional and physical toll of the disease. Shannon

wrote about how her treatment, which is supposed to help her feel 'normal', can actually foster the negative social isolation others mentioned:

> *While I am incredibly grateful for Hizentra, it has really reduced my ability to have a high quality of life. I tend to either be totally fine after each infusion or am very sick and extremely tired for 24 to 48 hours. This really led to issues with really being able to do things on the weekend and developing/continuing social relationships outside of work. It also caused me to not be able to do things like weekend yoga classes or different 5/10K runs on Saturday mornings out of the concern that delaying my infusion, even less than 12 hours, would impact Monday*.

While the focus of treatment is to improve the quality of life, the side-effects of treatment can have a negative impact.

While many individuals with PID felt fortunate to get a diagnosis and start treatment, not all were happy about their new situation. Monica shared her initial resistance to the diagnosis and treatment plan:

> *My response was, this is impossible, it cannot be, there's no way I'm going to have infusions. And then Doctor Y said, well, if you don't do it, this is what you can do, and this is what you well might be facing. Then she said, you're so lucky, particularly given your line of work and if you don't want to do the infusion now, then it's given this is in your future. So, I went from "there's no way I'm going to be doing this." And then of course she said we have to make sure your insurance will cover it. And I'm thinking "oh no, what if the insurance doesn't cover it. What's next?"*

These participants relay the anguish of having a chronic disease that, on a daily basis, permeates how they must live their life. Most express apprehension about doing too much and trying to appear healthy and normal to other people, knowing they may suffer consequences. In her journal entry, Megan explained the conflict she faces in deciding how much to do:

> *I have these ideas where I want to do more, but I am worried about pushing myself too much. I don't want to overdo it and then be sicker tomorrow. It seems like such a waste to have a little bit of energy and not be able to do anything with it. I tend to get sick, like once a month it seems. Around this time of year, I also start to get depressed. I think I*

> *have seasonal depression. Trying to deal with that as well. I think I sleep more when I'm depressed as well, because I don't want to deal with life.*

One of the most profound journal entries in this group came from Melanie, who explained:

> *I pushed through most of the weekend as we had a lot planned. I went out for lunch with a friend which was awesome...but boy did I pay for it last night and today. It was hard putting on the "healthy show," when I really just wanted to cry, curl up under the table, and take a nap. Playing "healthy" is exhausting!!*

The description of putting on a healthy show, and the exhaustion that comes from it, is profound. Many in the PID population seem to try to function as if they were healthy, perhaps an attempt to avoid acknowledging the gravity of their chronic disease.

Tara also described putting on a show, as she shared her attempts to stay optimistic during her treatments:

> *Every time I go in for my infusion, just like I did for my chemo, I'm the girl that's happy. The glass is half-full and I'm the happiest person in the place, but internally that depression is, "Oh my god!" Every single month that infusion comes faster and faster and here I am, gone for 6 hours again. Physiologically it can really do, it can really do something to your psyche, but I'm not the girl that it is going to put down, I'm the girl that's just going to say, "It is what it is," I'm going to bless my body, and share my story*.

As expressed by these participants, there are both physical and emotional ramifications for "putting on a healthy show." The concept expressed by these participants, that the chronicity of PID can be all-consuming, emphasizes the impact of this disease on them, both emotionally and socially.

The overwhelming feeling of fatigue. A predominant discussion point, with nearly every participant, was the overwhelming feeling of fatigue they experience. While fatigue has been discussed in the PID population for some time, there is limited evidence to quantify the topic. A recent study by Hajjar, Guffey, Minard & Orange (2017) examined historical patient records and found an increased prevalence of fatigue in individuals with PID, especially those with CVID

(which was the primary diagnosis of participants in this study). When asked about their fatigue, the participants in this study provided detailed descriptions about the degree and depth of that fatigue. Michelle explained:

> *It changes my personality. When I am fatigued, I don't want to talk to anybody, I don't want to be anywhere. I just want to be in my own little world and hope that it will go away soon so I can get my life back. So, it does definitely impact me and it's frustrating and especially when you can wake up day after day feeling fatigued and think, "is there any end in sight?" It really starts to wear on you. Just an overwhelming blanket, I don't know how to describe. Like heavy feeling. Just no matter what you do, if you rest it doesn't help, or if you close your eyes for a few minutes. When it's at its peak, sometimes the only thing I want to do is just go to bed and put the covers over my head kind of thing. It's very hard to motivate, to push yourself. And I guess that another description of it is you feel like everything is an effort. You have to just keep pushing yourself, keep going on when it's really bad*.

Her description reinforced the concepts of isolation and frustration, expressed by other participants throughout the themes presented. Tina tried to quantify the feeling in a way someone without extreme fatigue could understand, explaining: "*the best I could do to try and put it in relatable terms, is to tell them to think of the most stressful exam they ever took in school, then, kind of take it while running a marathon on 24 hours of no sleep. The feeling you would feel, during and after, might get close*." Tina's description shows the degree of fatigue she feels is only close to what she might experience at any given time; as she describes it, her fatigue reaches a level that is beyond quantifiable.

Melanie similarly struggles to explain her fatigue to her family in ways they might understand:

> *It sounds very ridiculous, but I said it is like walking around with some big men's shoes, but then, on a normal day. Then, when you are having one of your what I call "beyond fatigue days," I said I had to walk through a marshmallow floor. I said, "It's just, you just can't." You are just physically drained, and you are emotionally drained. I guess almost like a mourning type of thing. It is weird for me, I feel like this is bizarre for me to say it this way. But you know when you are grieving somebody, and you are just so into*

> *that, that it's like you can't really function beyond that moment. And I guess that's, in a way, another way I can describe how the fatigue feels. It is like almost like time slows down, then you feel drained and you feel heavy. It is hard to think of, "Oh! my goodness I have to think about making dinner tonight." You can't even think that far. Even if it is like an hour away, it is like you can't even think that far.*

Melanie described her fatigue as all-consuming. She also mentioned the concept of grieving, which was discussed by other participants throughout the study.

Dennis focused on the physical impact of the fatigue. Dennis described his experience:

> *Fatigue, inability to have energy for life and activities, various body aches and things that would be highly unusual, and rarely experienced, as part of day-to-day living before my diagnosis. It would be the thought of doing something is difficult and actually carrying that task out is triply difficult. An example would be where you debate about getting self-serve gasoline because you can't imagine having to get out and pump it.*

A comparison can be drawn between his current physical state and his prior level of function; here, the concept of a 'new normal' is evident. Life-altering issues relating to fatigue were evident during Michelle's interview:

> *It completely consumes me, and I've had times before I was diagnosed, and I didn't know what's wrong with me. I didn't know why I felt like crud all the time. It completely consumed me, it took over my life, it affected my quality of life. I just I was just tired and fatigued and miserable all the time. Thank God when I got my diagnosis, yes, it's something I'm going to have for the rest of my life, but at least I know what I have. I know that there are things I can do to help me.*

Connie describes the emotional and physical problems associated with her disease and how it impacts her inability to function at a level she expects of herself:

> *It is as much of a problem for me emotionally as it is for me physically, because I expect so much of myself. But, how I would describe it is the inability to achieve any of my goals. It's also the inability to focus. It hits me one or two times a week probably, and if I nearly feel it coming, like three weeks ago, as I was trying to get ready for the trip, I was so exhausted that I ended up leaving three days later then I intended to leave because I just couldn't pull myself together to get ready. Because I couldn't concentrate on what I needed to bring, and I couldn't concentrate on making a list, and I couldn't concentrate*

> *on putting in a couple of blogs before I left town. I couldn't concentrate on anything and I just kept laying on my bed and taking naps*.

Connie openly shared her disappointment in not being able to perform as she would expect and in being forced to adapt her plans, due to symptoms linked to her PID diagnosis. Leslie also mentioned how she struggled with fatigue impacting her ability to function:

> *Lethargic. I have a hard time keeping my eyes open. I can't concentrate on anything. I'm constantly yawning. I just feel like I have no zip, no energy, no anything, I just need to lay down. Sometimes if it hits me before I get home, like at work, I kind of sit down and kind of hold my head. Just trying to find a way to push through, until I can get home.*

The participants discussed how the fatigue they experienced is unrelenting; they often expressed frustration over their lack of control of the disease process. Kimberly described this feeling of helplessness as having, *"a list of things to do and I just look at it and it just seems like impossible, too burdensome, to do. Just can't even, you know, I don't get anything done. I'm just tired, and kind of beyond tired. The sleep does not make it go away. I'm too tired to get out of bed or function*. A similar sense of hopelessness was heard from Cynthia, who explained:

> *It feels like you're just so tired that you just can't get out of your own way, because you know you have things that you have to accomplish and have to get done, but you just can't get them done no matter how much you want to or how much you know you have this deadline or whatever. But, it's like even if you knew you can drink a cup of coffee, it's not going to help you anyway*.

Participants described interventions they tried to use to combat the fatigue, often without success. Megan discussed her attempts to pace herself, and methods to complete necessary tasks, when she was coping with the overwhelming fatigue:

> *I don't have enough energy to stand there and vacuum the house or do anything for longer than maybe 5 to 10 minutes and I get really hot and tired, have trouble breathing. I have to sit constantly. I can physically feel it, like my body feels like I weigh like an extra 100, 200 pounds. My legs feel like they're little. I start to sweat and start to feel a little shaky, almost like if you haven't eaten in hours and you just feel all hot and sweaty and shaky and just exhausted to the point of "I can barely keep my eyes open and I need*

> *to sit down." I don't necessarily need to nap, but I need to lay down and rest, to just lay there. So, I just plan for nothing, just lying in bed and just doing nothing. Nothing seems to help give me energy*.

The overwhelming nature of the fatigue was described as an emotional and physical depletion of energy from many of the participants. Claire described the feeling as eliciting sadness, or disinterest, when the fatigue was at its peak:

> *I feel like I have some weight on my legs and I just can't and then I get to the bed and can't even take a nap. When I'm in bed, it's like I don't even want to get up and go to the bathroom. I tend to get sad and, at least, melancholy, if not sad. I'm just like, "oh! this is not stopping," and I don't even want to watch TV. I don't want to do a puzzle, or anything. I just want to lay in bed and you know, just kind of roll over if I can't sleep*.

The participants in the study consistently described an overwhelming fatigue that was described by Amanda as "*a constant enemy, constant. I never wake up feeling good. Even on the good days, I still have that…I feel good, but I'm still tired.*" Amanda goes on to explain how fatigue never goes away:

> *You feel like you should wake up feeling better, but you just never feel like it's enough. I could just keep sleeping, and I've slept 14-15 hours before, and I just don't feel as if I'm well rested at all. And so, it's just a constant struggle in my life. My life would be totally different, I mean, that is my number one problem…like the Road Runner cartoon, and how the road runner and the coyote go along full speed ahead and then all of a sudden, I have an anvil dropped on my head or I run into a brick wall. It's like all of a sudden, out of nowhere, bam! It is just hits you, and it's crippling.*

Similar to Amanda's interview, Courtney described enduring fatigue episodes, which accentuated the underlying, daily fatigue she experienced:

> *It's like being shot with a sedation dart. It will hit me, when I have my, what I call my fatigue episodes. My daily fatigue is just like, you haven't slept in three days, where you are kind of dragging along. But, I will be like totally fine one minute when I have my fatigue episode, and then it feels like someone has shot me with a sedation dart and all that. I literally can't move. I am just collapsed wherever I am, and I don't know how to compare it, but I've been on an anesthetic, it is very similar to that, it hits you really quick*.

Lori explains the unpredictability and unrelenting nature of the fatigue she experiences, in her interview:

> *I hate fatigue. Fatigue is a big pain in the rear. I have always had a little bit of trouble with fatigue, even as a child. My mother would always tell me, that she dreaded whenever I was invited over to sleep overs because when I would come home, I would be a bear and I would be running a fever. As I get older it seems to be worse and that sometimes it would just hit, and it can be like this bone deep fatigue. Like I just, like my legs feel like lead. I can't hardly lift one step in front of the other. All I want to do is sleep and yet, no matter how much sleep I get, it is not enough. But then, it has to run its course and, after a few days, then it goes away…during that time of the fatigue I can't do hardly anything. I don't work outside the home…I don't think there is any way I could, because I never know when that fatigue is going to hit me. When it does I can't think straight, I can't make decisions, I'm just so exhausted.*

The unrelenting impact of fatigue on Lori's QoL, and associated issues with cognition, limit her ability to engage in normal activities, explaining:

> *For several days now, I have been extremely fatigued. Sleeping a lot, but I can't seem to get enough sleep. My mind has been foggy, hard to think. And I definitely can't seem to make decisions. I get like this every so often. Fatigue has been an issue with me since I was a child, but not to the level as the past couple of years*

Fatigue that slows her down and limits routine activities was also described by Marsha, who explained:

> *It just feels like I'm carrying a heavy weight of something. Everything takes a lot of energy, even to do little things, when it's at its worst. And something that would maybe take me 30 seconds to do, I can look at it and think, "I can't do that right now." And it's still there the next day and the day after that. So, it's not paralyzing, I guess, but it kind of just puts me into such slow motion that I'm almost stopped. That's what the fatigue does. Sometimes I think about, I'd really like to do this, but I'm not going to get up and walk out of the room and get it, it's too much effort.*

The fatigue described by the participants was never-ending, it was a constant partner; while it varied from day-to-day, they described the fatigue as always there. They perceived a kind of fatigue that could not be remedied, not by coffee, medication, nor sleep. Donna described her fatigue as:

> *A feeling of constant tiredness. Has nothing to do with wanting to sleep, it is like, it is so hard to describe because when I say to somebody, "I feel fatigued I'm extremely tired," okay take a nap. It doesn't go away with the nap. It doesn't go away with the coffee. It doesn't go away with anything. It is very hard for me to describe it. If I describe it, that's how I would describe it: extreme tiredness that doesn't go away with sleep or with…maybe you sleep eight hours and you wake up the same way, you know exhausted. That you don't have the energy to wake up*.

Jennifer spoke about her expectations that treatment would help her fatigue, but it had not, and her frustration was expressed during the interview*:*

> *My energy level is the same since my diagnosis, I was hoping that I would see an increase in my energy level, especially with starting my infusion medication. The doctor said that a lot of people do see an increase. I have not seen that increase in level. It is kind of disappointing, but for me this is all I know, and it has been my norm for years. So, I'm just hoping for a miracle. My fatigue feels like all day long like I just woke up 10 minutes ago. You have that sleepy, your body feels tired, sleepy, just want to take a nap all the time. That's how I feel all day, just tired. That level varies through the day. Sometimes it's just absolutely 100% exhaustion, sometimes I will take a nap at lunch during work. I will do that for my lunch break instead of eating lunch. Other days I'm just so tired, but I push through it. It feels kind of foggy sometimes*.

Just as there was consistency in the participants' stories as it related to cognitive impairment, there is consistency in their reports of the depth and oppressive nature of their fatigue.

Impact of chronic disease on emotional well-being. Chronic disease can impact mental health and emotional well-being (Turner & Kelly, 2000), which was another area of concern for many of the participants in this study. Tina shared her perspective, noting the unpredictability of the disease can affect her emotional outlook: "*I think it strongly contributes to the depression. Because when you can't function, you can't physically do things that you should be able to do, that you know you should be able to do. Or one day you can or one day you can't, the mental toll is massive."*

Melanie noted how the decline in her functional level has been a stressful process, leading to depression, when she considers how her life has changed: "*Looking back over the past year and a half, it is like I have noticed few things that have changed in the past year and a half, physically. So, it is kind of depressing in a way because I looked at what I used to be able to do before. It was very stressful, and it was stressful for me."* Linda also spoke about the depression associated with her fatigue and its impact on her QoL:

> *When I can't get up and exercise because I'm too sick, or I'm confined to, you know to the hospital, I guess that makes me down. More so because I can't…I'm not able to do those things. So, that can bring me down on multiple levels, not just physically, but mentally too, because I can't do it. A lot of times I push through the fatigue, but that just backfires*.

Several participants acknowledged the emotional impact of their medical care, treatments, and insurance issues in their journals. Tina shared:

> *Sometimes you do just need to give it a day. The constant ups and downs are so hard to deal with, but I keep clinging to the ups, which have actually been sticking around for three days now. I am making a mental effort not to stress our future, or what we are going to do. The medical care, or lack of, is never going to change here unless another hospital system finally moves in. We just hesitate to move right away again for the purpose of medical care. Medical is such a huge stressor though, I swear the number of things on my diagnosis list only keeps growing*.

Linda discussed the stress associated with medical care, treatment, and, in particular, insurance authorizations, noting they are: "*stressful and towards the end and the beginning of the year, or any time there is a change of insurances, it is stressful, because you don't know what is going to happen. Are they going to make you wait to get prior authorization? Because that has happened to me before."* Linda further described how navigating the healthcare system could be challenging and frustrating, especially for an individual with a rare and expensive-to-treat diagnosis, such as PID.

There is anxiety and stress associated with the process of being diagnosed with a rare medical condition, especially the process of understanding the disease and available treatments. For some individuals, learning about PID helped to alleviate some of the stress. Leslie shared the emotions associated with receiving her diagnosis:

> *It was scary, because I didn't understand it. And then, I will say my doctors at Johns Hopkins, were very good at giving me a lot of information. Medical journals and everything, just because I really wanted to understand. I will say, it in some ways it alleviated some stress for me, because I was so tired of being in the hospital and sick all the time*.

She also explained her frustration, by saying:

> *I would say living with a PID, is that everyone seems to think they know best for you. I find that very frustrating. Or they're like, maybe if you do this you wouldn't need to do that and it's like, no it doesn't work that way. And when doctors tell me that, "are you sure that's what you have?" I find that frustrating*.

The journal entries of the participants reflect how depression, anxiety, and stress impact their QoL. A straightforward and honest journal entry from Megan relayed how depression limited her activities, "*I have been more depressed lately. Makes it hard to want to do anything. Depression makes motivation difficult. I know exercise can help but it is so hard to get up and go*." Tina's journal entry exposes the depth of the depression she experienced during the study period:

> *The depression hit its worst again. I'm so sick of the up and down. I seem to get a little up and then go so far down, so fast, that it leaves me gasping for breath. All I want to do is curl up somewhere and just stay there forever. I'm drowning. I pulled out the bottle of meds that I never started taking a few months ago, but then I put them back in the cupboard and just went and cried. My reasons for not taking them are still the same. I am still breast feeding and I learned that they lied to me about them being safe for my baby; the stupid insert even says so. I hated how I eventually felt last time and the weight gain that started happening, which has turned out to be a common thing apparently. As if I didn't have enough issues being down already. I cried for a while and figured that we will see what tomorrow brings and go from there. I did make myself go for a short walk*

> *around the block. Nothing exciting but I know that if I don't do that much I may never get myself out of the house when I need to*.

Depression is not the only emotion that impacted the participant's emotional well-being. Tina's frustration about fatigue and physical limitations is evident in her journal, noting, "*I have more motivation to get things done, but I still ache and hurt so much that my actual productivity level isn't able to keep up, which is causing some frustration."* Similar to other participants, Melanie wrote about hiding the challenges she experienced, explaining: "*Struggling...just plain struggling. I'm trying to do some stuff around the house today and it is so hard! Tired, physically and emotionally. Pushing through is so difficult, but I don't want people to see how bad it really is. Not sleeping well is kind of taking its toll, I think*."

Melanie described in her journal how her frustration over physical symptoms caused her great distress:

> *Went in to help the teacher I work with to move our classroom down the hallway. I was fine until we started moving the big items...desks, boxes of books, toys, etc. I started to get really tired and dizzy. I almost went down a few times…finally sat on the floor, with my head between my knees. Suddenly, I got really hot and felt like I was going to vomit and started to shake. It was the strangest thing. I honestly didn't feel like I was overdoing it. I was drinking lots of water. "Why does CVID have to do this to me?" This dizziness seems to be happening more and more often. I'm just frustrated. I want my old body back! Anyway, instead of going for a walk this afternoon, I went home and took a nap. I'll try to go for a walk tonight*.

The question of "why me," expressed by Melanie relates to the concept of loss, including grieving, anger, acceptance, and denial, which are integral to coping with a chronic disease (Telford, Kralik & Koch, 2006). Individuals with greater control over the disease often demonstrate high levels of problem-focused coping; this includes information searching, problem solving, and direct actions (Folkman and Greer, 2000). Those individuals with less

control often utilize emotional-focused coping; this incorporates the concepts of escape and avoidance, need for social support, or distancing (Folkman and Greer, 2000).

Cynthia wrote about the need to let go of her anger, accept her situation, and focus on healing:

> *Now I am doing the right thing and getting all my stuff taken care of. No more putting things off for me. Maybe it's the nurse in me. The noncompliant patient, I mean. Nurses are some of the worse patients out there. I'm really trying to let go of the anger. I believe I still carry around some anger from my diagnosis. I am really focusing on healing and energy. I believe in order for that to happen, I need to let the anger go completely. I'm trying to be very mindful of that, but it's really hard.*

Cynthia's struggle to accept the reality of her disease highlights the impact of the diagnosis and symptoms. Perhaps, more importantly, it displays the psychological and emotional impact of facing the permanence associated with the life-long diagnosis of PID.

For some, like Shannon, the challenges associated with the disease were faced with optimism; she focused on maintaining a positive outlook, as described in her journal:

> *I am staying optimistic about HyQvia. It has made me more tired this past weekend and the previous one, but I know it is due to changing a medication and will only be once. I am still waiting to hear from insurance if it is approved…I cannot stress over things that I literally have no control over.*

Treatment elicited a variety of emotions according to the participants, especially if the treatment was not working as well as the individual expected. This was the situation for Cynthia, who expressed, "*I am feeling really down and discouraged because I am beginning to wonder if maybe the IVIG is not going to work for me? I am coming up on one year of diagnosis and ten months of IVIG infusions, and I am feeling worse than one year ago*."

Depression, anxiety, frustration, grief, anger, discouragement, acceptance, and optimism illustrate the breadth of emotions shared by these individuals diagnosed with PID. While there

are some that display a positive outlook, negative emotions are more prevalent throughout the interviews and journals, which appear to take their toll on the participants short- and long-term emotional well-being. Tara spoke about her struggle in admitting how depressed she was:

> *One of the interesting things when I started the program, I didn't realize how depressed I was. I did not, my daughter kept reminding me, but I really didn't want to admit that I was depressed. I'm not depressed any longer. Well, you are trying to function as normal human being, not sleep 12 or 14 hours. You try to sleep like a normal human being, you wake up and feel like you don't feel like a nap two hours later. I think the depression, that's part of that whole thing, also plays into the way in which you can or can't cope with fatigue. Fatigue is this little fire river that's ranging inside of you, and you're not really conscious of it, other than the fact that you feel like shit. You don't feel like yourself, you don't feel like going down and making dinner, or going to the grocery store. You don't feel like talking to anybody, you don't want to even pick up the phone and talk to somebody, and have him say, "Oh, mother it's so, good to hear from you, how are you doing?" I don't want to answer that question, because they won't understand*

The individuals in this study spoke about how they used to be better able to cope with the stress and anxiety they faced. Courtney explained the impact of ongoing stress:

> *Stress, I can't handle stress at all, which used to be, used to be I could handle it pretty well. But any kind of stress, whether it's good or bad, will set me back; it kind of just drains me. I try to compare it to like having a battery that's never fully charged and any kind of stress will just drain the battery and set me back. I might get sick or just feel really bad and have a bad day or few weeks. It all depends on how bad the stressor is*.

Defeat, regarding the diagnosis and accompanying fatigue, was an emotion best explained by Angela:

> *I have only tried the power of my mind, positive affirmation and stuff, and like I said, I can break through it sometimes. Just like telling myself, "You can walk 2 miles, you can," and then after walking I feel empowered. So, it just keeps going and going, I feel great about myself and my disease. Sure, I feel sick, but then eventually it all falls apart and I'm just so tired, I don't even get dressed. Some days I stay in my PJs, and I hate that, but I do it*.

The emotional impact associated with concern about getting sick, making choices regarding treatment options, and anxiety over the cost of care was shared by many of the

participants. Maureen explained, "*Fatigue and energy, and then there is a level of anxiety about exposing myself to other people's illnesses*." The high cost of IgG replacement, either in the form of IVIG or SCIG, caused a significant amount of stress and anxiety for many individuals with a diagnosis of PID. Jennifer shared the impact of the high costs of treatment:

> *The only thing about being on infusions that is super stressful, is at the end of this year… and the insurance changes, trying to qualify for some of the financial aid that they offer, which is amazing. I wouldn't be able to do it if I can't get the aid, so every year, in the back of my mind, that's another huge stress. It's like, "will I qualify again?" And every time they increase the dose, "will the insurance company approve it?" They bill my insurance $6,000 a month, I mean there's no way I can afford that out of pocket.*

Lori's anxiety and worry during the diagnostic process is indicative of the uncertainty associated with the disease.

> *When I was first diagnosed but before treatment, I was a nervous wreck and I didn't sleep much at all, because I didn't know what the insurance company was going to say. I didn't know how the treatment was going to be, I was just very, very nervous, so I was not sleeping very well at all. I was maybe getting about four hours sleep, which for me, is not good.*

The utter hopelessness and extreme exhaustion associated with the disease is expressed by many, and is clearly evident in Maureen's journal:

> *I could not do a thing all week. I am just exhausted, depressed, sleep is all over the place. It is too hot for me outside until around 7:00 p.m. but no energy to do a thing. I cried and cried around four a.m., after not being able to sleep. I slept from 6:30 a.m. to 10, but feel like I am dying. How can anyone be this tired and something not be REALLY wrong and not just some chronic thing?*

The emotional strain on those with a chronic disease can be exacerbated by the loss of a friend or family member due to the disease. The loss of a community member with PID can put the issue of mortality in the forefront for these individuals, evoking a significant emotional response, as expressed by Marsha, in her journal:

> *Lost a vibrant member of the CVID community to an upper respiratory infection this week. I am feeling sad about that. Someone in a Facebook group asked what emoji would work for CVID. One person suggested a big vacuum cleaner that sucks away so much from life. Sounds about right*.

A journal entry from Cynthia spoke about the loss of a friend with PID to suicide:

> *Emotionally, physically. We lost a zebra sister from our Facebook support group to suicide. I'm just devastated. She was the second person I met. I didn't know her death was suicide for sure in the beginning. It touched me to my core. I guess I don't blame her. I have no thoughts of harming myself, no worries, it's just I can see how people want to end it all. To not do this anymore. It's just heartbreaking. My heart breaks for her mom, her family, her grandmother she went to see before her death. It's just shaken me*.

Impact of chronic disease on QoL and activities. The various facets of chronic disease, including the physical feeling of fatigue and the emotional impact of anxiety, have a significant impact on QoL and the ability to participate in activities (Megari, 2013; Tóthová et al., 2014). Maureen described the negative impact of fatigue on her ADL and IADLs:

> *About twenty years of fatigue. It has really affected my parenting and my work…that kind of thing. So, how it affects me now is, I'm just in bed too much, whether I'm already awake or not. It's just, I can get to where I almost can't take care of myself. So, if I have obviously eaten…and I try to eat clean, so there is a lot of chopping and a lot of dirty dishes involved…quite a lot of work involved with doing that. Or, I'm too tired to go to a doctor's appointments and now I have to pay $25, for not cancelling early enough. And it's just such a vicious cycle because it's causing me expenses I don't have money for in the first place*.

For Lori, her diagnosis impacts her ability to do everyday activities, making her "*unable to do the things I want to do…plan activities…or I have to cancel last minute*." She described the disease as making her "*feel miserable*" and having to be proactive in protecting herself from germs in her environment that could cause her to get sick. She explains what it is like to protect herself, often depending on her husband "way more" than she likes.

> *If I was at the store, and someone was coughing in the aisle I would turn around and go the other way. I would make a big detour around anyone who was visibly hacking, blowing, or sneezing, or whatever they are doing. I have become more aware of just how*

> *many surfaces that people actually touch that are not cleaned regularly, even in doctor's offices, even in my immunologist office. I might have dismissed it easily because, you know, everybody has got germs. I wouldn't have thought any of it, but now, I know I have to be more careful and I don't think I'm a fanatic, just much more aware than I used to be*.

There was discussion about the need to prioritize personal resources by many of the participants in this study. The amount of activity each participant could tolerate varied, depending on whether it was a good day or a bad day. Courtney explained how she often needs to make hard choices about what she is able to do on a given day.

> *A good day is, I can take a shower, I can go to the grocery store. I might be able to walk my dogs around the block. I can go to an event at my child's school, I can go to a family function…you know, all of those things are luxuries right now. So, that would be a good day. When I can do something like that, get the laundry done, sweep and mop the floor, all of those are good days. Bad days, I really can't get out of bed, that's pretty much it. Then, I have the in-between days. I can get out of bed, but I can't really do anything other than just kind of daily functions: feeding my dogs, feeding myself, and kind of going from the bed to the couch, the couch to the bed. Sometimes I can't drive because the fatigue is so profound it is as if I'm sedated. My husband is a truck driver, so he is on the road all the time. So, I'm home alone most of the time. My older son is in college, I may have to have him go do something for me or go pick something up for me, or run the errand I was supposed to do, because I just can't do it. Or, I can't take a shower, I have to decide whether: am I going to do the dishes today or am I going to take a shower today. Sometimes, I just have to choose. I have to prioritize from what needs to be done and do that*.

Variability in the ability to engage in daily activities is also described by Amanda, who explained:

> *It's okay. It's not great, but it's not horrible either. It kind of fluctuates from day to day. Some days I'm having really good days. Some days I have really, really bad days, so it depends. A good day, I wake up feeling really good, I have a lot of energy, and I am able to go about my daily life, and without too much problem. To be able to do my job, go home, maybe exercise, maybe cook dinner, and go to bed at a normal time, that's a good day. A bad day is, I wake up and, pretty much from the moment I wake up, I don't feel good. I have a headache, or I'm really fatigued all over. I'm struggling to just kind of*

> *get out of bed. I kind of drag through the day. I go home and almost instantly hit the couch because I can barely keep my head up*.

Fatigue also forced some of the participants to modify their activities to meet life's obligations. Donna, who works as a psychotherapist, shared how she is learning to recognize her own limitations and modify her activities. Her struggle to accept the limitations imposed by the fatigue she experiences is on-going, as she explains in her interview:

> *That is a big, big, big issue. Sometimes, I feel so fatigued in the morning, I cannot wake up, I cannot leave the bed. Sometimes I need to stop my car in the afternoon, not nap you know, but relax a little. Then, sometimes I really want to do things, you know, and the fatigue just stops me. Sometimes I am okay, and I can do everything. Trying to listen to my body, it is very hard for me to…I listen to my body, but I don't pay attention. I want to keep going like nothing happened, and I'm getting to the realization that I cannot do that. Whenever I think that I can keep going, you know, I cannot do it anymore*.

Jennifer manages to conceal her limitations at work, but she shared that she often suffers the consequences for pushing through the day when she returns home. Her efforts to cope with those limitations are evident in her description of the unrelenting emotional and physical toll the disease is taking on her and her family.

> *I feel it the most physically. Just always tired, emotionally as well, depending on the level of stress. Mostly it is just physical and energy level, you know. I just wish I had more energy, more pep in my step. People don't know at work. I just push through and do my job, I'm pretty tough. At home, on the weekend or evenings, I just I crash. I just want to take a nap. I take a nap every day on the weekend because I'm so exhausted. I can't function in a day without a nap. On the weekend it just seems like I crash and burn, every time Saturday rolls around. I think it prevents me from doing the activities I like to do with my kids. I find that, "oh gosh I have all these great plans for us during the weekend," and sometimes it depends on how I'm feeling if we actually venture out and go do anything. My little guy, he doesn't know the difference. My older one, I think we always took him out and did more things. I have never really thought about how it wears on me emotionally, I know the stress probably wears on me more, but the fatigue…I have had it so long. Now I just don't pay attention to it that much, other than it is just constant, and it is always there. Some days I just push through it and other days I'm just tired and I just give up, and I just chill. I have had it for so long, it is my norm*.

Tina also elaborated on the challenges of trying to push through:

> *That one is a double-edged sword, because it's given me a reason finally, which is a relief to have an answer and so we can have an idea of where to look for help. Reduces some of the issues, but at the same time, it almost feels like it became an excuse. Because before, I would try to push myself more and well, if I just do this maybe it will help, if I just do that maybe it will help. Now I know most of those things are not going to do it.*

The physical and emotional impact on the ability to perform activities was also made clear in the interview with Susan, who explained:

> *The smallest things are an effort to get done. As an example, my mother lives in an assisted living facility and she gets around with the help of a walker and oxygen. And there are lots of times that I have to go pick her up and take her to a doctor's appointment or take her for shopping…the thought of having to pick up her walker, put it in the back of my car multiple times, is almost overwhelming*.

Some of the participants reported modifying their activities, even basic ADLs, but they also report that on good days they often forget those limitations and suffer for it later. Angela shared:

> *I don't do any house work, I don't cook, I don't do laundry, my husband does everything, literally. I feel like I'm one of the balloon guys in front of the car dealership, the car dealer guys. They are all filled with air in there, flapping around in the wind…you know what I'm talking about. That's what I feel like normally and I fantasize flapping around and then it feels like somebody unplugged me, and then I just collapse, and I'm down for a couple of days or weeks. I cannot have a shower and do my hair and make-up on the same day if I have an appointment for something. So, I will shower the night before, wash my hair in the sink the next morning and try to get myself pulled together. My fatigue is really hard to break through, and then once I do, then of course I think I'm super woman…I try to do everything and then I'm down again. I haven't learned to balance it yet*.

The journal entries confirm the challenges of performing routine activities and the consequences of doing so. Marsha had multiple journal entries that highlight these issues, noting in one: "*Today I ran out of undies and was down to the orange socks (means everything else is dirty). I had a dryer full of clean clothes from last week that I had not retrieved because I didn't have the energy to go to the basement."* In another journal entry, Marsha expresses her

dissatisfaction with her QoL, "*I believe that my QoL will be affected long-term, but it is really due to the fatigue. My former doctor told me to live my life and do the things that I enjoy. I'm sure I would still enjoy lots of things, but the energy to do them is missing*," and "*Maybe forcing myself back into portions of old routines will do more for my spirit. And for my laundry situation*." Finally, as noted by others, she also wrote about the fear of getting sick and the subsequent social isolation when maintaining life-long activities, explaining: "*I have not been attending church for a long time, as I am concerned about the crowd and germs. I went last year, and some people prayed for me with their hands on my shoulders. I came home with a respiratory infection that lasted for many weeks.*"

Many participants reported that they tried to push through the fatigue, frustration, and anxiety associated with their chronic disease, often without success. For many participants, this brought about feelings of guilt, frustration, and disappointment that they could not participate in family or personal activities. Lori explains in her journal:

> *It was very hard to wake up, I feel very tired and don't want to over-do as we have a trip to the zoo tomorrow with the grandbaby and kids. I haven't been this tired in a while. I'm trying to learn to listen to my body better. Today feels like a day where I had better listen, but I feel very guilty for not doing my exercises, especially the new ones*.

Lori also wrote, "s*ince I was already tired, I had to push and haven't completely recovered yet. Have so much to do today, but really just want to take a nap. Probably should*." Her comments send a message about the emotional toll of the inability to push through the fatigue. There is a hopelessness she conveys about her situation. This perception of hopelessness is sometimes further promoted by healthcare providers, such as the one seen by Donna: "*I went to the PCP this week to discuss my fatigue, she told me you have CVID and Sjogren's, nothing can be done about your fatigue and pain*." The ramifications of the physician's statement to someone with a chronic disease seemed to be overwhelming for these participants: "*nothing can be*

done"…nothing. It is important to consider the psychological impact that the words this physician used may have on this individual with chronic disease. Rather than assuming that there are no solutions to the fatigue and pain experienced by many individuals with a diagnosis of PID, healthcare providers may need to think holistically and explore non-traditional or non-pharmaceutical interventions for this patient population.

Brain fog. Many participants in the study discussed a cognitive impact due to fatigue, anxiety, and chronic disease. This cognitive impairment was consistently characterized as forgetfulness, word finding deficits, and difficulty processing. Kimberly described it as:

> *Part of, I'm forgetting what I'm doing or why I went in the room, I think everybody does that. I used to be a very detailed person. I could keep everything in my brain going, I could keep track of all kinds of dates and things. Now, if I don't write it down and look at it, like if I don't have a list or something, I probably would just totally forget it*.

Likewise, Cynthia explained her cognitive impairment:

> *Well, it could be like I forget things, things that aren't clear to me. It could be like really bad as far as with word finding…other times it could be just as simple things, "what is it that I did yesterday at two o'clock in the afternoon" or something silly like that. Or, like my family will say I'll repeat things. I'll say something and then maybe a few hours later then my kids will say mom, you already told me that. I'll be like, yeah, okay, and they'll say it's your brain fog again.*

Similarly, Megan described her experience with forgetfulness and word-finding deficits:

> *I have a very hard time finding words when I'm speaking and it's, since I've been diagnosed, I've been avoiding talking on the phone or talking to people because I can't…like, it's on the tip of my tongue or I can see the word in my head, but I can't get it out and I just feel so…I feel really stupid. I have to write everything down. Like, I have a journal that I write, I try to write in every day, especially if I'm going to go to the doctor, because I'll go to the doctor with like three questions and I'll forget like half of it when I get there. Because I just get side tracked or I just don't remember*.

Leslie attributed her cognitive impairments, particularly her ability to make decisions, as being impaired when she wasn't feeling well:

> *It seems like I can't focus on anything, I can't process anything. I don't like to make decisions because I don't feel that I'm being rational or processing them in a way that might be advantageous, when I start to feel better, when I look back on it. For the most part, my brain is still really sharp, because I can remember things pretty well. Then it's like I can't even concentrate on driving*.

Maureen described her experience with cognitive impairment in detail:

> *It is a lot of brain fog. So, word finding can be difficult and then just…I was trying to book a flight, for example, to see my daughter in California, and I tried three times and I can't sit through the task. It is just a little too overwhelming with the dates around my infusion, and how many nights, and I just haven't been able to do that, and she doesn't understand. That can be debilitating. I mean at the very worst, I have actually been in my car, and forgotten which thing is the blinker, and which is the windshield wiper? That kind of a blip in your memory, you know, it upsets me.*

Courtney spoke about very similar cognitive symptoms in her interview:

> *All of a sudden, it's just this brain fog comes over me. Or, if I'm having a bad day, it is just hard to remember things. Because I also have a reminder on my phone, even if it's for just really basic stuff, like to call the doctor and schedule an appointment or to call, I have to put reminders down for everything now, which I never had to do. My memory, and my recall, is not what it used to be or where it should be*.

Marsha focused on the deficits surrounding word finding, especially frustrating to her, given her prior level of advanced education:

> *Sometimes I can't think of a word, a word that I know very well, and sometimes I use other words to go around it, so that people don't know I'm struggling with that word. Or, people will ask me what something means, and all of a sudden, it's gone. It's kind of embarrassing sometimes when I can't even think of basic words*.

Word finding deficits were also the primary experience for Tara, "*That right there is probably one of the most frustrating experiences, to not find language, when you are so used to be able to carry on conversation."*

Angela reported experiencing agnosia when discussing common objects, which she described during her interview:

> *Well, I forget what I'm talking about, as you can see, and I can't retrieve it. Somebody has to tell me what I just thought. I forget how to do things. The most frightening thing that I forgot was, my husband was telling me he was going to build something and put plastic sheeting over it and I thought," plastic sheeting, what's that?" He says, "oh! You know what it is, it's all over the place." And I thought no, I don't know what it is. We went back and forth and finally he pulled out some saran wrap and said, "it is like this only really thick." I went, "oh my God! I can't believe I didn't remember what plastic sheeting was." It will be things like that, and I think he has to remind me several times a day to take my meds*.

Although participants understood, and often made light of their forgetfulness, this previously unexplored symptom appeared to influence many aspects of their lives. It is not clear as to the cause of the cognitive impairments that are reported by the participants in this study, and there is no literature that would help to explain the symptoms reported by the participants in this study. Donna felt her deficits were linked to her fatigue, which she described was worse when she was due for another IVIG treatment:

> *Sometimes, for a while, I was infusing every four weeks, and by the third week, my concentration my memory, was getting terrible. I was sitting with a patient, and I couldn't remember what words…"ah, ah," because I couldn't remember the words that I wanted to tell them. It is terrible. And it is the same, sometimes it is like I go blank, you know, and it is like I need to Google to see what is the word that I wanted to say. Memory and attention, in general, gets worse before infusion and fatigue*.

Lori described how she frequently needed to adjust her energy output; she wrote about her discouragement, "*this morning I woke up clearer and was able to walk the dogs. That is probably it for the day. I can feel my brain becoming somewhat foggy and so will probably need a bit more rest. It's very discouraging*." In contrast, Susan described the same symptoms, and went for further medical evaluation due to the history of Alzheimer's disease in her family:

> *I was sent to a sleep neurologist because I thought I was actually developing Alzheimer's disease, because my cognition had become so poor. But I was diagnosed with sleep apnea, so it's probably stemming from that. Memory is a huge thing. Just forgetting that I told this one or that one something or that they told me something and just have zero memory of it at all. Not even with hints am I able to retrieve it*.

While she attributed the symptoms to her recent diagnosis of sleep apnea, there is a similarity with her reported cognitive symptoms and those of the other participants; this presents another area of research that needs to be explored with the PID patient population.

The cognitive impairment experienced by these participants was described by Amanda as anxiety-provoking: "*I will say, a lot of memory problems. I don't know if that's just fatigue or what, but I do struggle with memory issues. I get brain fuzzy, I get overwhelmed, anxiety-feeling, easily. I don't know if that's just tiredness or it is the PID.*"

The consistency among the participants, as related to the cognitive impact they describe, has not been documented in the research literature relating to PID. It is unclear if this cognitive impairment is a function of the disease process, or if it is linked to their fatigue and emotional state. These descriptions focus on clearly defined symptoms of short-term memory impairment and word finding deficits; this is not something that has been previously discussed in the research associated with PID.

Theme two focused on the physical and emotional challenges of living with a chronic disease. The participants described the negative impact of the social isolation; social isolation contributed to depression and negative emotional well-being and reduced the potential for expanding their support group. The overwhelming feeling of fatigue was mentioned by nearly all participants in the study; this fatigue negatively impacted their ability to participate in ADL and IADLs, social activities, and reduced their QoL. The participants also discussed the negative impact that their chronic disease had on their emotional well-being, QoL, and activities. Finally, a new finding in this study was the report of brain fog; many participants in the study experienced similar episodes of forgetfulness, reduced short-term memory, and word finding issues.

Theme Three: Facing stigma…"We are not faking it." The third theme that emerged from the interviews and journals, is about the participants perceptions of having to face the stigma associated with an invisible, chronic disease. Individuals with PID have a serious chronic disease, yet they are often told "you don't look sick." This brings up what, exactly, should a sick person look like? It is important to consider if there is a stigma attached to chronic disease that implies if an individual looks healthy on the outside, they cannot be seriously ill. The concept of "healthy" may be a reflection of the individual's unique perspective of health, disease, and illness, that is shaped by their personal experiences, cultural identity, and personal relationships (Iwelunmor, Newsome and Airhihenbuwa, 2014). These factors contribute to an individuals' perception about illness and illness behaviors. For example, Courtney identified herself as the "*sickest, healthy person*" you will meet. During her interview, Kimberly explained:

> *People don't understand rare disease. I look fine. I push myself, then I get overtired, then I get sick. I mean no one gets that you do infusions and sit in a chair for three hours and you are tired the next day, and all that stuff. I think they just have to see it to figure it out. I don't look sick so therefore, I am not*.

This was echoed by Grant, who noted:

> *Basically, it mostly impacts me socially because a lot of the people you talk to on a daily basis seem fine. They don't have to deal with issues that you do. You kind of just pretend like everything is okay and then, if you try to explain yourself, it usually is met with a "oh okay" or "that sucks" or just a generic response that you're expected to hear. It definitely has impacted me the mostly socially because nobody can quite comprehend what I have.*

There was a feeling expressed by several participants that other people do not understand what they are going through.

Many people, including medical professionals, have a limited knowledge of PID (Waltenburg, Kobrynski, Reyes, Bowen & Khoury, 2010) and often lack an understanding of the disease and its ramifications. Connie expressed concern about the lack of knowledge in the

medical community about her PID diagnosis "*When I chose my primary doctor, after I got diagnosed, I told my primary what I had, he told me he wasn't comfortable treating me anymore, because he knew nothing about Primary Immunodeficiency. So, I actually interviewed three doctors before I picked one.*" Several participants communicated that they found it challenging to justify and prove their disease to others, but to have to do so with a medical professional was even more disheartening. Shannon explained how she feels about having to get medical professionals to take her seriously when she believes she is developing an infection. Because she looks healthy on the outside, and the medical professional may lack an understanding of the impact of PID on the immune system, she explained how some healthcare professionals may assume she is malingering or exaggerating her symptoms. It is not uncommon for this to happen to patients during the diagnostic process, and again, throughout the course of the disease. Shannon shared part of her story during the interview:

> *In retrospect, I wondered why no one ever tested it when like I had gone to the doctor multiple times a month. But my entire life was just random crazy infections. So, there were times, especially when I was in graduate school and we only had access to student health, where I was accused of being, it was actually in my medical records at one time, that I was a hypochondriac. Because that was very disheartening, and I think when I was re-diagnosed, it was kind of affirmative that I wasn't insane, and that there was a reason behind that symptom. And it wasn't because of being a hypochondriac. I find issues with doctors thinking I'm too complicated or either that I'm exaggerating because I'm not just going to sit and complain. I think it's really good to have an explanation for medical providers, so they don't think I'm crazy. And even if they don't know what it is, I think it at least, that then I follow up with I'm immune compromised. But I think it gives them some sort of reference that there's a reason I'm not feeling well.*

Other participants mentioned that family and friends do not understand what they go through, from both a physical and an emotional standpoint. Dawn spoke about how her husband unintentionally communicates that he thinks she is acting sicker than she actually is:

> *Other times it upsets me is when my husband thinks that I'm being, like, he doesn't mean it, he'll say something to indicate, he doesn't mean to indicate it, but it's like I chose to*

> *do that, I chose to sit in bed all day. Where I'm like, I didn't choose to sit in bed all day, I wish I could get out of bed and do whatever I want to do, but if I don't sit and rest right now then it's going to be a hell of lot worse for a hell of a lot more days. Then he will say, "I didn't mean it that way, honey." And then I say no, it just sucks because it's hard for him as a caregiver for us too.*

Her comments also relate to the stigma associated with living with a chronic disease. However, this participant is also experiencing the strain and burden a chronic disease places on the caregiver or family members.

Having expressed feeling a stigma associated with their chronic disease, participants expressed relief when they were finally diagnosed as having a PID. The formal diagnosis was a validation that they had a real condition, and their symptoms were not imaginary. Melanie talked about her relief when she was finally diagnosed, and she learned she had a real condition:

> *First, I think it helped in a way, because it kind of made you feel like, "oh! Wait a minute, I'm not crazy." Because you knew something was wrong, but I guess it was frustrating just not knowing. But after the diagnosis, I would say in relation to those, I would say that in a way, it kind of helped the quality of life, I guess. Just having the diagnosis and that type of stuff, because I could at least point my finger and say that's what the reasoning is, that's why I am not feeling 100%, that's why I can't do whatever*.

Likewise, Megan also expressed relief at being diagnosed:

> *Having the diagnosis was a relief to know that all the times I've been getting sick there is a reason for it. I'm definitely…I still get sick, but it's better than it was because I'm not getting as sick. Having the diagnosis helps. I'm more reliable in being sick. I'm not faking it. I'm not just a person looking for drugs or, you know, I'm definitely sick. I'm not faking it. So, with before getting sick all the time and I was just like, I don't know what's wrong and doctors before were just like, "we have no idea what's wrong with you." So, they just gave up on me, but now that I have a diagnosis it's like, "okay. We know we can treat it*."

Melanie also recognized that having a diagnosis made it easier to explain her situation to others, especially her family, as to why she needed to limit her activities:

> *I would say that in a way, it kind of helped the quality of life I guess you could say. Just having the diagnosis and that type of stuff. But at least I could point my finger and say*

> *okay, well that's what the reason is, that's why I'm not feeling 100% and that's why I can't do whatever. But at least I can say to my kids, this is what it is, and this why mommy feels crummy a lot. So, this is very stressful, very stressful. Up to that point, now it's what I call a different stress, where you just worry about how you are going to feel every day and not worried about, 'Oh! Well kids want to go for a hike this weekend,' and how I'm going to do this, and how can you save up enough energy to be able to do stuff like that or that type of stuff. It's a different stress now.*

The self-doubt that arose when medical professionals were not able to provide an answer for the symptoms experienced was described as frustrating by these individuals with such a rare disease. Instead of finding support and answers, they felt they were met with doubt and denial from the professionals charged with helping them. Tina shared how she was expected to "get tougher" in dealing with her symptoms, prior to getting her diagnosis of a PID:

> *So, the last seven months have been incredibly interesting trying to find doctors who have a clue, yet alone have even heard of CVID. Before I think I was better at hiding how absolutely hard things were, because I got tired of being told I just needed to suck it up and get tough and, you know…if I just do this it will get better. So, I hid things so well but then I was sick so much more often*.

Often, the delay in diagnosis, or lack of understanding of the disease, led to a delay in treatment or to a worsening of the symptoms. Those who found a medical professional with appropriate knowledge, or the drive to search for answers, believe they have been fortunate. Unfortunately, they may be in the minority, given the long length of time until diagnosis for many of the PID population (Chapel et al, 2008; Joshi et al., 2009).

Recognition that the participants were not making up their symptoms, that they were not "faking it," was key to their emotional well-being. Even though they may still face the stigma of "you don't look sick," having a verified medical diagnosis was a validation of their symptoms. Courtney spoke of the feeling of validation in her interview:

> *It was a kind of a relief, because I have been going to the doctor for so many years and being told "there is nothing wrong with you, you are absolutely fine, having low IgA*

> *doesn't mean anything. Be glad." It was a validation, maybe that's the word that I'm looking for. The validation that, like my family has always said, you are the sickest healthy person I know, because I never drank, done drugs. I don't eat fast food. I don't drink soda. I eat so clean, and yet I was always sick. I started to think, "gosh, am I just lazy?" Like I just want to lay around all the time. But I know that I don't. I want to be out, I want to be running, I want to be training, horse-back riding, I want to be mountain biking. You start to question your sanity, so to get the diagnosis is like, "yes!" I want to send it to my old doctor who said, "it doesn't mean anything, you are fine." and say, "really, here you go*."

Mixed emotions in having disease validated but trepidation in knowing what to expect was a key part of the interview with Angela:

> *At first I just thought "oh! Give me a pill." I was excited that finally somebody figured out what was wrong with me, because obviously I have been sick my whole life. I got diagnosed with rheumatic fever as a kid. I got diagnosed with fibromyalgia as a young adult, and then the CVID. It made me feel really good. It validated all those trips to the emergency room and again, like I told you, the more I learned about it, I actually said to the immunologist, I said, "so I'm I really sick? Really, really sick." He got mad at me for saying that, he said, "don't say that, you have a disease." Then, like I said earlier, after digesting all the information, it made me feel pretty rotten, to tell you the truth*.

While some participants focused on validation, others focused on the sense of relief the diagnosis brought them. Lori talked about relief for having a treatment that would help her feel better:

> *Well I'm not really stressed about the diagnosis, because for one thing my sister had it before me and I could see how it improved her life when she started feeling better, with the treatment. Being diagnosed with a disease does not really bother me, as long as there is treatment. But being diagnosed was actually a relief, because I knew then it wasn't in my head, like so many doctors had thought*.

The relief for Dawn was having an answer, a diagnosis that was not the disease she had feared in watching her mother suffer.

> *It made me happy, actually. I was being told that I was an enigma for so long, and there was nobody like me, and nobody had idea what was wrong with me. That when is it was finally determined what it was, it was like a relief. I grew up with a mother with multiple sclerosis, so, I'm an autoimmune nightmare with other stuff. So, it was like I was tired of*

> *being told nobody knew what was going on and that it was in my head. I would say the diagnosis brought a great relief to me.*

Amanda found relief from both the validation of her symptoms and the potential of treatment:

> *I would say honestly, in some ways I feel like it's more positive because I finally have a name for what's going on with my body. Because I've spent years of going, "why am I always sick, why am I miserable, why do I feel like this?" And you start to think you're losing your mind and then you finally you have somebody go, "well actually no, you're not crazy, there's actually something wrong with you." In some ways it was like, "oh, a relief," because it was like, finally, there's something wrong with me and they can pinpoint it and they can give me something. And there's a doctor that said, "yes, there is something wrong with you." The illness is a relief, because you get so crazy. You go crazy*.

These participants suffered from real symptoms and recurrent illnesses, often for many years, before they were finally diagnosed. They expressed an emotional toll from having to repeatedly prove their illness, over and over, especially when they looked healthy, even normal to others. As many participants explained, they are normal, but it is a 'new normal' to them; it is not the same 'normal' as they had prior to their diagnosis.

The journal entries also confirmed the feeling of being stigmatized by participants due to having a rare disease, their need for validation of the diagnosis, and the lack of knowledge encountered from medical providers about PID. Shannon made several journal entries concerning the topic, as she had recently relocated and was searching for new healthcare providers, noting, "*I was able to connect with a new primary care provider after a bad experience with the first one here. I appreciate having a doctor to listen to my concerns, respond to them, and not treat me like a hypochondriac because I don't have a fever*." She continued to write in her journal:

> *The only thing that is really increasing my stress is getting all the doctor appointments set up, still from moving here (and, subsequent cost) and waiting for referrals. I also haven't had too much luck finding a new primary care doctor; I found a nurse practitioner but would feel more comfortable with an internal medicine doctor and/or*

> *someone with experience with primary immunodeficiencies or similar disorders. The nurse practitioner is open to the "off-market" things that help me feel better, but she hasn't been great with follow through (ex. TENS unit for migraines, continuing B12 shots for fatigue/migraines). I'm going to give it one more appointment--she listens, so that is a positive*.

Megan also expressed frustration in her journal, relating to the lack of medical providers who are willing to listen and believe in the seriousness of her symptoms:

> *I dealt with the pain and GI stuff for a couple days but had to go see my immunologist on Thursday. He offered no help. I was very disappointed in his dealings with me. He basically didn't believe I was having adverse reactions. He kept saying I needed to go gluten free and dairy free. THAT'S NOT THE PROBLEM. I was so pissed off. He seriously blew me off. So, his solution was to start me on either IVIG, which I need my port for and he doesn't like, or another subq [SCIG treatment]. He arranged for me to try another subq [SCIG treatment] which will be weekly. I'm unsure of what to do*.

The interviews and journal entries from the participants express the emotional impact felt when they feel their voices are not heard by their medical providers, family and/or friends, particularly in understanding they are "not faking it" and have a real disease, with real consequences.

Theme Four: Exercise is exhausting…"Wanted to exercise, but just too exhausted."

Many of the participants in this study were excited to start a new exercise program. Their initial outlook about what exercise might do for them was positive, and they were eager to try something that could make them feel healthier. The participants perceived exercise to be beneficial and felt it would help to reduce their stress and improve their QoL. However, some of the participants struggled to stay engaged in the exercise program, while others reported that the exercise made them feel more fatigued. Some participants reported frustration in not being able to sustain the exercise program, especially those who engaged in high intensity, long duration, high frequency exercise prior to their diagnosis.

Research has shown that physical activity improves mood, especially for those with anxiety and depression (Peluso and Guerra de Andrade, 2005). When asked for her perspective about exercise, Jennifer said, "*I think it definitely impacts your health, and makes you feel a little healthier. It just gives you a little bit of energy for that day. I think it's good for you, it makes you happier."* Marsha expressed, "*I think exercise has the potential to increase anyone's quality of life. To me, exercise has to be something enjoyable. When you're doing something that you enjoy, and it is healthy for you, that has to make your quality of life better*. Monica emphasized the importance of exercise for her emotional well-being; she expressed that exercise is, "*absolutely critical for mood and energy. If I don't exercise, I'm not a very happy person*." Donna also found that exercise had an impaction on her emotional health, *"oh! Yeah, emotional, it releases stress, and I was doing it with a friend, and the thing is, walking with a friend and talking. Then, with just that, it was good to release stress*." Exercise has been shown to positively impact physiological and psychological aspects of the body; this includes the release of endorphins, improved mood state, increased self-esteem, and reduced stress (Mikkelsen, Stojanovska, Polenakovic, Bosevski and Apostolopoulos, 2017). Amanda described the physical and emotional changes she saw when her sister committed to a routine exercise program; these were changes she hoped to experience for herself. She explained:

> *I honestly really believe that exercise can do a major change. I have seen it with my sister especially. She had a lot of depression issues and she started running and it has changed her, not only physically but also emotionally. She loves running, she runs marathons now, and that is her especially happy place. And so, I definitely believe in the power of exercise, but I haven't gotten to a point where I can feel like I can do it consistently.*

Several participants found exercise to be stress-reducing. Carl explained:

> *I'm getting into a routine of taking a brief rest after each exercise session: this is turning out to be a nice stress-reducer. Another benefit noticed, no ill effects experienced after*

> *starting the formalized program of daily exercises tells the subconscious that I'm leading a healthy life, in spite of whatever may be going on with the immune system.*

Carl was one of the participants who surpassed the suggested exercise frequency and duration and experienced no negative effects. As the oldest participant in the study, yoga was his primary means of exercise and he regularly practiced meditation. He found ways to modify the exercises that would allow him to continue to participate in something he considered to be a healthy behavior. Carl was also diagnosed much later in his life, as compared to many of the other participants in the study. Jill, another supporter of exercise, expressed that exercise gave her something to which she could look forward to. Exercise helped to reduce her stress by getting her out of the house and reduced her social isolation:

> *Well, I was very excited at first, because I could participate in that…it was good, because I made at least three times a week. I need to get out there and walk. That was maybe something to look forward to and to kind of work on. At least, I just need get out of the house, and that's good. I feel like it helps to reduce the stress. When I had a neighbor in the hospital, I walked with him. I make sure make sure I still do that. I'm kind of gave me something to focus on and work towards*.

Angela also used exercise to explore her local area. Participating in exercise program helped her recognize the activities she was still able to accomplish, providing a connection to her prior self. She shared her thoughts about her participation in the exercise program, noting, "*in general, I felt really good about everything. It brightened my outlook. I was outside doing a river walk, along the river. It's helped me get out of the house and helped me know that I can still do physical things*." Angela also described how participation in exercise allowed her to reduce her social isolation, explaining:

> *Again, by getting me out of the house, I didn't walk alone, I met a new person at the mall. This person is actually a marathon runner, and he choose to walk with me as a cool down. I met a friend so, socially, that was a step up, being out in the beauty of nature. Like I said, I have to have some help walking along the river. Just the feeling, moving my entire body. Exercising, you know you are using everything, really, it's by all means and*

> *muscles. Your heart beats a little faster. So, I've been aware of how my body felt, and I felt fit. But then, people started saying "you're walking too much, you are not ready for this." I ignored them for a while*.

Angela struggled with the exercise program, though she stayed engaged to the end of the program. She had some weeks where she was able to meet her exercise goals and other weeks where she struggled to get out of bed.

For several of the participants, the exercise intervention was a motivator. The exercise intervention gave Lori incentive to get "active," as she explained in her interview:

> *I have really enjoyed it, it did exactly what I was hoping it would do, which was kind of to motivate me into getting active again. I used to be way more active until I just started getting sick, moody, and everything. I know I had the type of personality that sometimes I need a little bit of competition or to motivate me to get things done, and this exercise study definitely did that. So, I was glad to be a part of it, even if there were days I didn't feel like doing it, and I didn't do it. I was still thankful to have it.*

Lori had to face the reality of managing her disease symptoms and recognize that she was not able to consistently participate in the exercise program and be as active as she once was. Unfortunately, while some participants agreed that the idea of an exercise program was motivating, they also found that they became more fatigued after participating, even at a low intensity. While the participants were emotionally committed to participating in the exercise program, many found that they physical symptoms of their disease were too burdensome. They wanted to exercise, but the physical and emotional ramifications of their chronic disease restricted their participation. Jennifer described her experience during the exercise intervention:

> *I started out super excited, super motivated, I'm always a big procrastinator. Like I said, trying to balance work, home. I get to work at 6:30 in the morning. By the time I pick up the kids, I get home at six, almost six o'clock at night. Trying to find time to do it now that I'm back in school…you know, homework stuff, dinner, trying to exercise a little bit. My thing is like, I can't exercise super late because it is going to keep me awake all night. I did that once and it was awful. I didn't sleep all night for a few days. So, I started out with high hopes. I wanted to be more flexible than I am, because I feel like I'm this old*

> *woman at 43. I felt good the days that I did exercise. I felt like a sense of accomplishment, then I found the next day I was just tired. I was not motivated*.

Jennifer reported that she "*did feel a little bit more energized and positive, but it just seems like it would make me just, even a lot more, tired than I said."* In her interview, Courtney also described the range of emotions experienced by participating in the exercise intervention; this included her initial excitement, then dealing with the reality of her limitations, and ultimately persevering and achieving a sense of accomplishment:

> *The past few weeks, I was so excited to have an exercise program to do. You know it was like, I have a reason and an excuse that I have to work out. The first, if I remember correctly, the first two or three weeks I don't think it was bad, it was fine, I didn't overdo it. Then I started feeling, I think I started having…I was feeling so good that I was so was overdoing it and then I couldn't do it. I couldn't work out for week. I found that when I did do it the first couple of weeks, it was really helping me. When I start feeling good, then I would just overdo it because I never know if it is going to be two weeks before I feel good enough to do this again. So, I will just kill it one day, feeling great and just do everything and then overdo it, and then pay for it for a week. That is the hard thing, the hardest thing is pacing myself, and just doing 20 minutes of yoga, not 20 minutes of yoga, 20 minutes kettlebell, taking a walk around the block, mopping and sweeping the floor, vacuuming and doing the dishes, do the laundry, you know what I mean. I'm like, "I'm feeling great, I feel great I'm working out." Not letting it be, I have to add on, add on, and add on*.

Courtney describes the challenges in pacing herself, something she never had to consider before her diagnosis. The struggle of adapting to these new limitations and a change in lifestyle proved to be challenging for this participant.

Even though she experienced fatigue and discouragement in the early part of the exercise intervention, Lori also reported a positive experience. In one of her journal entries, she wrote:

> *I'm sore from my exercises yesterday, but it's a good feeling, shows me I need to keep it up. I was tired, but we went anyway, and I felt recharged though drained a bit in the evening. I remember thinking as I was on the trail that if I had stayed at home I would have taken a nap. So, it was good for me to get out. I was nervous that it might make me sick again, as I've only been off antibiotics for a bit. Time will tell*.

Lori's reflection also highlights the constant fear of living with a chronic disease; her interview conveyed her concern about becoming sick again, even though she only participated in what most people would consider to be 'normal' activity. Despite experiencing the increased fatigue, similar to other participants, Lori persevered:

> *I feel better after my exercises than I did before. I was not feeling like doing them at all. Tired, not in the mood, and draggy. But I did them and it helped! My mood is better, I'm proud of myself for doing them. Though I could really tell my energy level was down... my forms were not great, out of breath quickly*.

Her dedication to the exercise program paid off over the eight-week study period. What started as discouragement turned into a sense of accomplishment. She learned to manage her fatigue and continue with the exercises throughout the study. Lori shared her perspective:

> *Well, at the beginning when I could hardly do anything it was a discouragement and I made sure to stick with it. It made me feel a little bit more confident, even though with some of the exercises I feel very sore. I kind of like that soreness, because it tells me that it is working*.

Participation in exercise helped the participants improve their physical and emotional well-being. When Lori was asked to describe her level of physical well-being, she replied, "*I would say good, even though I would be sore, like I said, I didn't mind that soreness, I liked the feeling of accomplishment that it gave me*."

Courtney shared her optimistic viewpoint, likely the result of having a diagnosis that was more recent; she still hoped to return to her prior level of 'normal'. Her journal entries focused on her love for exercise, even if she was not able to participate at her previous level. Courtney wrote:

> *I am a bit depressed over the setback and hope I can at least get back to where I was earlier this year. I guess you never really appreciate what you <u>can</u> do until you can do even less. I still LOVE exercise...well, the thought of exercise at this point. I dream of running my 5Ks and 10Ks and cycling for 20 miles as I did before. Nothing will ever*

> *dampen my enthusiasm for fitness, but my body and health might prevent me from participating as much as I would like*.

She also shared how she had to learn how to pace herself during the exercise intervention, described in her journal, "*I've enjoyed starting to exercise again. It brings back memories of when I was training and competing. I'm a bit anxious if it will cause me to crash, so I'm trying to take it slow and easy - hard for a former competitor*." In contrast, Susan was not happy about having to pace herself. She enjoyed exercising but felt frustration over not being able to exercise at her previous level of activity, explaining:

> *Well, like I've already said, if I'm able to get out there and get some exercise in, I am happy. Happy is not the right word. Because it's never at an intensity level that I would want it to be at. It's not near the intensity level that I once was able to work out at. But there's something about just getting outside and being able to clear my head in the fresh air. Even if it's just for half an hour, it's beneficial to me*.

Carl enjoyed having a variety of exercises to explore through the exercise intervention, as he explained, "*being able to handle new exercises, and continuing to feel good, reinforces the idea that PID doesn't necessarily limit the variety of one's activities*." He further elaborated that being able to exercise helped him to not focus on his disease and also helped him feel a sense of normalcy. He continued by saying, "*yeah, in the sense that if you don't exercise you start feeling like you're going to be sick for the rest of your life. Exercise gets you on the road and thinking about things other than diseases.*" Interestingly, as the oldest participant in the study, he was the only one who routinely practiced mindfulness and cognitive behavioral therapy; he attributed his positive outlook on life to his commitment to those therapies. His participation in an exercise program gave him an opportunity to feel 'normal' again and allowed to reconnect to his prior self, who he recalled was an active and energetic individual.

Despite the positive outlook about exercise from many of the participants in the study, there was also a sense of frustration, fatigue, pain, and discouragement. Angela started the intervention feeling excited and motivated. Unfortunately, she also became discouraged and frustrated when she was not able to maintain her pre-morbid level of duration and intensity of exercise, explained during her interview:

> *The exercise program really helped me get motivated again about being healthy. I was very excited about it, and I set goals for myself to reach. I got home and started a walking deal. And then, when I couldn't reach the five miles, I was very frustrated. Plus, I was in pain and I got fatigued, very fatigued for a long time after. My hips and my knees are just now starting to feel better. It really helped me, because I hadn't been pushing myself like I always did, pushing myself.*

Angela's experience emphasizes the challenge of adapting to a 'new normal' and having to adapt the activities she was once able to do with ease. She continued to express her frustration over her physical limitations in her journal entry, "*yeah, maybe I'm only supposed to increase it a little bit instead of walking five miles and walking out. I swear to god that day I thought I was literally going to die. I could not touch my hair, I was dripping wet, and I had run out of water*." Frustration over her limitations was also clear in the interview with Courtney. She described how exercise had always been a key part of her identity, and the frustration she felt in not being able to participate at the same level of intensity level as before:

> *It was hard to answer the questionnaire because I wanted to answer it with, how I normally feel. How I felt a few years ago, compared to what actually happens to me now. My perception of exercise, in general, and in me when I'm working and I'm well, is fantastic, and it is core to who I am. It is part of my identity, it is so important. My whole family does it, every morning, I will go out and do five miles worth of track. It is just ingrained in me, that exercise is part of life, and I love it. I love working out. I love staying in shape. I love training for shorter times. I was never a distance runner, I was always a sprinter, but I did a half marathon and it was so bizarre. Because I trained for four and I only did one, but every time, I would get in training right before the half marathon I would get sick. Go figure, I did complete one and it was awful, because I just was diagnosed with the immunodeficiency problem. The 5K was were where I could*

> *really shine, and it wouldn't crash me. I'm hoping I can get back to that. I have a very positive view of exercise and I feel frustrated to not be able to do what I used to do. I mean I used to run and cycle thousands of miles a year.*

The feeling of frustration was also felt by Amanda, as she explained during her interview:

> *I feel honestly like I really didn't do much, because I honestly didn't exercise much. Honestly, I barely was able to do anything, and I hate that. It frustrates me, because I wanted this to be an avenue to get me back into shape, and feeling better, and that was my hope. But I got so sick and had so many rounds of antibiotics and what not, it was just too much. When I get sick, I swell in my throat really bad, and it causes me to have trouble breathing. So, needless to say, I can't do a whole lot of exercising.*

Discouragement was another strong emotion shared by several participants in the exercise intervention. Courtney also experienced challenges trying to participate in the exercise program during inconsistent weather. She shared her discouragement, writing:

> *I've had a pretty rough week. Losing more weight, no energy, no appetite. Feeling pretty crappy. Haven't managed to do even any walking since 10/22, so a week now. I'm feeling pretty discouraged and low. I don't know whether to attribute this to the exercise I have been doing or to the change in weather (it's gotten much colder this week, and I usually feel worse when it's cold or very hot), but it's not fun to feel so drained. I'm lucky if I brush my hair or put on a bra. And I'm very lucky if I can manage to take a shower. I feel like I'm going backwards in my health journey and it's depressing. All I want to do is run and hike and ride horses and ride my bike…heck, even take my dogs for a walk. Not been a good week.*

The frustration and discouragement expressed by these participants shows the emotional impact on their sense of self in not being able to perform at their prior level of activity. The participants in the study conveyed that successful completion of an exercise program can bolster spirits, while discovering limitations and barriers can result in greater emotional distress. When asked about her experience participating in the exercise intervention, Tara stated, "*I have no mental ability to even go there, I thought I could, but I didn't*." She struggled to complete the exercise intervention and came to realize the degree of depression she suffered from during the process. The emotional distress over not being able to function at a prior level of activity was

evident Susan's journal entries: "*Slept poorly, wanted to exercise, but just too exhausted. Simply not true that you can "push through it" if you just get going.*" She went on to express, "*absolutely perfect weather for running but CANNOT. Very depressing. Running used to be an effortless joy.*" Another journal entry reads, "*really miss running like I used to (marathons). I guess that person is gone.*" Her journal entries continued to express frustration and despair over her current situation, "a*ctually jogged some and felt ok. Not sure why though, probably last gasp of the runner I used to be.*" Finally, another entry read, "s*tress level is high, and exercise is very difficult. Quality of life is typical, but well below my 'pre-CVID' life.*" These entries from Susan were recorded at various times throughout the eight-week study period and show the continuum of despair at having to acknowledge her loss of identity; she conveyed a sense of mourning for her prior self.

Fatigue was a significant barrier for many participants participating in the exercise intervention. Lori explained that some of the days, she was able to push through the fatigue and complete the exercises. However, there were other days when it was not possible for her to even attempt the exercise intervention:

> *A tiredness that I would think anybody would have. I was able to still do the exercises and push through. I would feel, I guess, somewhat better afterwards. But when I got into these days that were really bad fatigue, I couldn't do the exercises. So, I just had to wait until it went away, there was just no way I could do that. I mean I could go on if I were just to walk from room to room, but there was no way I could do the exercises, and I was sleeping a lot*.

Donna wrote in her journal, "*walked a few times during the week, attended the Hollywood Bowl, stairs up and down. My energy level is not so good. Tired of being tired.*" Another entry expressed "*fatigue is almost always my company*." Her comment "tired of being tired" spoke

volumes. During her interview, Donna explained how the fatigue limited her ability to complete the exercises:

> *You know what, fatigue…when I am fatigued, is like everything, I don't feel there is anything that makes it worse or better, you know what I mean? It is like the fatigue is there. When I am not fatigued, I was feeling great doing it. When I was too fatigued, I couldn't even do it.*

Fatigue was a common barrier for Jennifer as well. Her approach was not to give up, but to participate at a low intensity level, by just walking. She expressed frustration that she was not able to participate at a higher intensity level and reach some of her goals, but she remained committed to completing the intervention. She conveyed this experience in her interview:

> *But I just couldn't handle one more thing, I was done. I was like completely at the end of the trail. So, for me, I need to accomplish my own personal goal is planning to do it, a solid three days a week, every week. I guess as much as I…I did a lot of just walking, I wanted to do like you want…cardio, lose weight, burn more calories, then, sometimes all I can muster is a walk.*

Lori expressed guilt because of the times her fatigue limited her participation:

> *It was very hard to wake up. I feel very tired and don't want to over-do as we have a trip to the zoo tomorrow with the grandbaby and kids. I haven't been this tired in a while. I'm trying to learn to listen to my body better. Today feels like a day where I had better listen, but I feel very guilty for not doing my exercises, especially the new ones*.

A journal entry from Marsha described how she must now force herself to exercise, when it used to help her feel invigorated:

> *I am completely exhausted. When I get a day that I can rest, I need to rest. Yesterday, I walked to the school twice for the boys, but I just couldn't make that third afternoon walk. I used to feel better after exercising or taking a long walk. Now, I have to force myself to do it, as I start out with an empty tank. I hope some energy will find its way to me soon. This is no way to live*."

Her ending comment "this is no way to live" speaks volumes; it clearly shows her frustration and despondence about her ability to complete her normal activities, much less include exercise in

that daily routine. The difficulty in facing what they can and cannot do, the reality, is emotionally draining and inherent among these participants' struggle; they want to hold onto who they once were, and who they would still like to be, rather than accepting who they are now, an individual with a diagnosis of PID.

Some participants were concerned that exercising would make their fatigue, pain, or illness worse. This was the case for Susan, as she explained:

> *If I were not listening to my body and I push myself every day…if I continue to run long, hard distances or I continue to lift heavy weights at high intensity, like I used to, then I think I'd be much worse than I am now. I think that my joint pain would be way worse. I think that my fatigue level would be way worse. I think that I would have way more breathing illnesses, because I would be so run down*.

Susan, who was an avid marathoner prior to her CVID diagnosis, acknowledged the negative impact of not being able to participate in a routine exercise program. She expressed, "*for me and my husband, exercise has always been an integral part of our lives, and not being able to do it is a real negative*." However, Susan also went on to describe the negative effects that exercising too much had on her QoL. She described this in her interview:

> *I would say that I think I went into it hoping that I would be able to exercise the eight weeks through and not have anything negative happen. But I've had days where I haven't been able to exercise and felt unwell or I've had full blown illness. And I think I went into it a little bit starry-eyed. But the reality of my life is that, I didn't need to see the study or to be a part of the study to really believe that hard exercise affects our disease. I think that if you work yourself in such a way that you're compromised, then it negatively affects you.*

Tara spoke about her experiences with exercises, "*when I worked out I was in so much pain, I didn't recover*." While Tara did not have pain, she found that exercise increased her fatigue. She wrote about the fatigue in her journal, "*right now, I am horribly fatigued. It seems like the more exercise I get, the more exhausted I am the next day*." Amanda struggled with more frequent

infections when she exercised. Despite her hope that exercise would have a positive impact, she described her past experiences:

> *Previously, every time I exercised I would get sick. I don't know if that's a coincidence, if that's mental, I don't know. But, I would hope that it would impact in a positive way. But, everything I've seen, it seems like, when I do exercise, I get sick. But, I don't know if I would get sick whether I exercise or not.*

Recovery time, post-exercise, is an important consideration for individuals with a diagnosis of PID. Exercise is expected to improve QoL (Pedersen and Saltin, 2015), however, if it is causing an exacerbation of pain and fatigue, modifications need to be made to that exercise program, or there will be poor compliance. The participants often spoke about the challenge in finding a balance between their activity level and the exacerbation of their symptoms.

Some participants described the challenge of finding enough energy to participate in an exercise program. They acknowledged their lack of motivation to complete a formalized exercise program. Dawn admitted her distaste for formal exercise programs, "*I think the main thing was I'm not a huge fan of exercising ever, I like to do activities that I like to do."* She went on to share more about the activities she enjoyed. However, she also described extreme fatigue after participating in those activities:

> *I won't really do anything that makes me tired. If I'm going to be tired, I'd rather do something with my kids. When they say they want to go for a hike, then I'd rather do that. The days that I was doing exercises, by myself, I did it, and that was fun, but it really didn't make me say, "oh! Boy this is so different, let me do this every single day." But, I really did enjoy Arizona, I enjoyed biking, taking the kids horseback riding…that kind of stuff. I like being able to do activity then… I was tired by the end of the trip. I had to take a wheelchair and I couldn't walk while I was at JFK [the airport], it was too much for me*."

Dawn described the challenge of participating in an exercise program when she was often struggling to complete her basic activities. She explained:

> *Well, I don't feel very good about it because of the fact that I have gained a lot of weight. I've almost doubled in size in the last couple of years between all the medicine and the inactivity, and I don't feel like I can do a lot of activity. I feel so bad a lot of days. I'd say probably three or five days a week, I'm just struggling to just do my daily life. So, because of that, I end up not feeling like I'm able to exercise. I'm doing good to just fix myself dinner. And so, physically, I feel like I've deteriorated over the years, because of just the plain inactivity.*

The participants in the exercise intervention willingly shared the challenges they experienced. Their frustration was evident, through the interviews and journal entries, and they shared their feelings that exercise was not an instant solution for their symptoms of fatigue, pain, and illness. Carl summarized this when he said, "*that might have been because everybody says, 'exercise is the wonder drug, it fixes everything.' Well, it didn't. So, I may have been a little discouraged at the beginning about the ad hoc exercises I was inventing*." Amanda summed up the consensus of the participants, noting "e*xercise helps, when I feel good enough to exercise*."

Many participants found the exercise intervention helped to motivate them, reduced their stress, decreased their social isolation, and directed their focus away from their disease. For some, there was a sense of frustration that they were not able to engage at a higher level of intensity, and that they were forced to pace themselves. Most participants did find that they continued to have fatigue which, at times, interfered with their ability to successfully complete their exercise goals. While many participants found the exercise program to be motivating, stress reducing, and beneficial in helping them to focus on their abilities, it also discouraged them by forcing them to face their limitations and the reality of having a diagnosis of PID. Although most participants recognized that exercise should be beneficial, they unfortunately often lacked the physical and emotional energy to engage in enough consistent exercise to reap those benefits.

Summary of Results

While there were no statistically significant results in the quantitative data analysis, there were trends in the data. An important finding was that all participants in this study scored below average as compared to normative population-based standards for the SF-36v2 QoL measure, at both measurement points in the study. This was especially evident in the General Health domain of the SF-36v2, for all participants, at both time points. There was a clinically significant decline (based on the established MID) in the Physical Component Summary score of the SF-36v2 for the control group, at the end of the eight-week study period. The participants in the exercise group reported more fatigue and stress over the course of the study, though this was not statistically significant. The exercise group also recognized more barriers to exercise and showed a trend towards a lower self-efficacy for exercise, as compared to the control group; again, this was not statistically significant. It is possible that with a larger *n,* statistical significance might have been achieved in some of the domains measured.

The fact that there was no significant difference in the number of infections or medical visits, to a variety of providers, between the exercise and the control group is a positive finding. It appears, from this data, that participating in an exercise program did not result in a significant increase in the number of infections or medical visits during the eight-week study period for this group of participants.

For the qualitative data analysis, four key themes emerged for the participants as it related to their stress, fatigue, and QoL: redefining normal…"not the person I used to be"; living with the challenges of a chronic disease…"it's hard putting on a healthy show…I want my life back"; facing stigma…"we are not faking it"; and exercise is exhausting…"wanted to exercise, but just too exhausted." Overwhelming fatigue is one topic discussed by many of the

participants; fatigue is also discussed in the literature about PID (Hajjar et al., 2017). However, the topic of brain fog and cognitive impairment, which was also a frequent discussion point, has not been explored in the literature.

These themes help to better understand the experience of an individual with a diagnosis of PID. Chapter 5 will explore the interpretation of both the quantitative and qualitative results in greater depth.

Chapter 5: Discussion

Introduction to the Chapter

This research study was a mixed-method, randomized controlled trial with two groups. Participants were randomized (via permuted block randomization) to either a control group or an exercise intervention group. The purpose of this research study was to explore the impact of a low to moderate intensity exercise program on stress, fatigue, and quality of life (QoL) in individuals with a diagnosis of Primary Immunodeficiency Disease (PID). This chapter provides an in-depth discussion about the quantitative and qualitative findings; these findings are generally consistent with the literature for other chronic diseases. A conceptual framework was developed to better understand the continuum of living with PID, specifically, the evolution of a 'new normal'. This chapter explores the limitations and delimitations that may have impacted the results of this study. Recommendations for future research and implications for practice are summarized.

Discussion

Stress, Fatigue, and QoL

Both quantitative and qualitative data was utilized to answer the research question that investigated the impact of an exercise program on stress, fatigue, and QoL. Data collected from pre- and post-study outcome measures (SF-36v2, FIS, PSS-10, EBBS, SEE and SEES), interviews, and journals were triangulated to assist in developing a deeper understanding of the experiences of the participants in this study.

For all quantitative outcome measures, there were no statistically significant results between the intervention and control groups. This is likely due to the small sample size (n=34).

By not rejecting the null hypothesis, because of the lack of statistical significance, there is potential for a type II error to occur. Despite the lack of statistically significant findings, there were several distinct trends in the quantitative data, which related to stress, fatigue, and QoL. These trends suggest that both groups experienced a high degree of stress, elevated fatigue, and poorer QoL. The participants in the exercise intervention group displayed trends towards more stress and fatigue, as compared to the control group. While the exercise intervention group did not experience a physical decline, which was reported by the control group, they did experience a trend towards greater mental and emotional decline. There was one finding of clinical significance in this study, based on the minimally important difference (MID), established through normative population data for the Short Form 36, version two (SF-36v2). Since many of the outcome measures used in this study do not have established MID values, it is possible that there are additional clinically significant differences present in the data.

The qualitative portion of this study sought to understand the experience of participants diagnosed with PID as it relates to stress, fatigue, QoL, and exercise. The study explored the perspectives of the participants to better understand the individual, and collective, experience of those with a diagnosis of a PID. This was accomplished through analysis of journals and interviews, completed by participants in both the control and exercise intervention groups. Four primary themes emerged from participants' interviews and journal reflections that expressed their perceptions of how the disease impacted their stress, fatigue, QoL, and ability to exercise. Theme one was redefining normal, "not the person I used to be"; this theme addressed the participants' thoughts surrounding their identity and self. Theme one included several subthemes: redefining a 'new normal', a loss of identity ("who am I"), recognizing personal limitations and adapting to lifestyle changes. Theme two explored the challenges of living with a

chronic disease, where participants expressed how “it’s hard putting on a healthy show…I want my life back!” This theme included several subthemes: social isolation; the overwhelming feeling of fatigue; the impact of chronic disease on emotional well-being, QoL, and daily activities; and the experience of brain fog. Theme three was about facing stigma (“we are not faking it”). This theme focused on facing the stigma participants felt was associated with having an invisible, chronic disease. Theme four expresses how exercise is exhausting, and although participants “wanted to exercise”, they were “just too exhausted” to do so. This theme focused on the participants desire to participate in an exercise program and their belief that exercise is beneficial. However, participants also emphasized how their fatigue interferes with consistent participation in an exercise program, their recognition that exercise does not seem to directly impact their PID, and their frustration that they were not able to exercise at their desired level of frequency or intensity. This finding is consistent with research that examines exercise in the chronic fatigue syndrome and related patient populations (Loy, O’Connor, and Dishman, 2016; Nijs et al., 2013).

The participants in this research study reported a high degree of stress, which was shared in both the interviews and journals, and through the Perceived Stress Scale-10 (PSS-10). Their stress came from many different sources, including emotional issues resulting from coping with a chronic disease diagnosis. There was also stress due to overwhelming fatigue, social isolation, and alterations in their lifestyle. Navigating the healthcare system, fighting for insurance authorization, and obtaining expensive treatments also contributed to an increased stress level for the participants in this study.

In addition to the interview and journal reports of stress, the PSS-10 was used to assess the perceived stress levels at baseline and at the end of the eight-week study period. Higher

scores on the PSS-10 are indicative of higher levels of perceived stress (Cohen & Williamson, 1983); while there was individual variability in the PSS-10 scores, overall, the scores for both groups indicated high stress. At the end of the study, the control group demonstrated a decrease in their PSS-10 score, while the exercise group showed an increase. This indicates that the participants in the exercise group experienced more stress, as compared to the control group, while engaging in the exercise intervention.

Based on the data collected from the interviews and journal entries, several participants in the exercise intervention group expressed frustration and anxiety over their inability to achieve their personal exercise goals; they experienced further distress over recognition of new physical limitations, as compared to their prior exercise ability. This chronic stress and anxiety may be linked to activation of the hypothalamic-pituitary-adrenal (HPA) axis; HPA axis activation has been correlated with increased pathological inflammatory responses (Chen et al., 2017). Exposure to acute and chronic stressors has been connected to sensitization of certain behavioral and physiological responses (Belda, Fuesntes, Daviu, Nadal and Armario, 2015). Instead of adapting to this constant stress input, these participants may be overwhelmed with the physiological and behavioral responses to stress. To respond to this potential lack of adaptation, stress reduction and management interventions should be considered by healthcare providers when developing a plan of care for a patient with a diagnosis of PID.

Fatigue was a constant and overwhelming presence described consistently in journals and interviews and confirmed through the quantitative findings using the Fatigue Impact Scale (FIS) and SF-36vs2. Most participants provided a detailed and vivid description of their fatigue. They acknowledged that their fatigue often limited their participation in activities, contributed to social

isolation, decreased their QoL, and impacted their emotional well-being; this was also evident, and confirmed, through the results of the FIS and the SF-36v2.

The FIS is divided into three subscales: cognitive, physical, and social. Higher scores on the FIS translate to a higher degree of fatigue (Fisk et al., 1994). At the end of the study, the control group demonstrated a decrease in their total FIS score, while the exercise group showed an increase. The trend towards an increase in fatigue among the exercise group may indicate why these participants experienced more cognitive (concentration, memory, thinking, and organization of thoughts), physical (motivation, effort, stamina, and coordination), and social (isolation, emotions, workload, and coping) impairments, as compared to the control group. Furthermore, participating in the exercise intervention may have contributed to this higher level of reported fatigue.

Participants reported that the fatigue and stress negatively impacts their QoL. Overwhelming fatigue was heard over and over, during the participant interviews, where they provided vivid descriptions to illustrate the depth and longevity of the fatigue they experienced; this fatigue was often a daily occurrence. Their fatigue was repeatedly described as all-consuming and non-responsive to any type of intervention. It impacted the participants physically, and emotionally, and had a highly negative impact on their QoL and ability to participate in everyday activities.

Throughout the journals and interviews, the participants spoke about diminished concentration and memory function, reduced motivation and energy, and issues with coping, in addition to the overwhelming fatigue. A MID score for the FIS has been estimated at 10-20 points for individuals with multiple sclerosis (Rendas-Baum et al., 2010). While PID is not the same disease as MS, they are both chronic diseases influenced by immune function, and they

share similar co-morbidities of disease and psychosocial implications associated with a chronic illness. Using the MID that was established for the MS population, the MID was not achieved, for either group, in the FIS total score, or in any of the subscales of the FIS, during this study.

One of the participants summarized the key impact of living with a PID as, "playing healthy is exhausting." This statement appears to capture how daunting the fatigue is for these participants and the scope of the challenge they face in trying to act as what they consider to be 'normal'. These participants expressed their perceptions of a reduced QoL and a heightened degree of fatigue, compared to what they thought they should be experiencing if they were healthy and free of their PID diagnosis. Diminished QoL was consistently noted in this study. While not all participants labeled their QoL as poor, they all described their QoL as less than optimal. They attributed their decreased QoL to the physical and emotional impact of their PID diagnosis, social isolation, and alteration of their perceived 'normal'. The PID diagnosis had a substantial impact on the participants in this research study. While many participants found ways to cope with their diagnosis, they still described a struggle with the profound physical and emotional impact on their lives.

The SF-36v2 was used to triangulate participants narratives that described the impact of their disease on their QoL. One very important trend, seen in the SF-36v2, was that all participants with a diagnosis of PID (regardless of group) scored below average (at times far below average) for all domains, as compared to normative population data. This highlights the impact that PID had on QoL for the individuals in this study. This was especially apparent in the SF-36v2 domain of General Health, which is used to assess overall health status. In this domain, all participants in the study scored exceptionally low, as compared to normative data, and compared to the scores for other domains of the SF-36v2. This is consistent with findings from

prior studies by Tabolli et al. (2014) and Quinti et al. (2012), which also noted low scores for General Health. While both groups were below the average, the participants in the exercise group demonstrated a slight improvement in their scores over the course of this study; this may represent an improved outlook on their health status, due to participation in the exercise intervention. This is consistent with current research that indicates that there is a positive association between physical activity/exercise and HRQoL (Bize, Johnson, Plotnikoff, 2007; Brown et al., 2004; Penedo and Dahn, 2005). While the participants in the exercise group may have experienced more stress and fatigue, they also recognized an overall improvement in their general health status or QoL.

The SF-36v2, Physical Function score, showed that those with a diagnosis of PID had a below average performance of, and significant impairment in, physical activities, as compared to population norms. This brings up a question of whether an eight-week exercise program is long enough to effect a change in the physiological performance of a chronic disease patient population. The literature is unclear about the length of exercise dosing for chronic disease populations, with some studies showing changes in less than eight weeks, and others requiring several months (Latimer-Cheung et al., 2013; Gibala, Little, Macdonald, and Hawley, 2012; Pedersen and Saltin, 2015). At the end of the study period, there was no negative impact from the exercise intervention on physical function in the exercise group. A small decline in physical function was observed in the control group, but not the exercise group; the exercise intervention may have prevented a decline from occurring for the exercise group.

Additionally, there was a clinically significant decline (based on the MID) for the control group in the Physical Component Summary (PCS) score. The below average scores, for both groups, for the PCS scores, suggests that those with a diagnosis of PID have greater limitations

in physical functioning, higher levels of pain, and greater restrictions in participation in normal activities due to physical impairments, as compared to population norms. Since the exercise group did not demonstrate the clinically significant decline in the Physical Component Summary score, it is suggestive that participation in the exercise intervention was beneficial. Exercise has been established as being beneficial, especially for chronic medical conditions; this is consistent with research supporting the use of exercise as a first-line treatment for chronic disease (Pedersen and Saltin, 2015). For some conditions, the prevention of a decline may one day prove to be as valuable as having a measurable improvement.

The participants in this study shared the challenges they experienced in adapting to their 'new normal' and in trying to not let their diagnosis of a PID define them. Several participants referenced a desire to feel like a 'normal' person, which seems to indicate they see their life as 'different' from others without the disease. There was also discussion about grieving the loss of their old identity and questioning who they now were; the participants expressed a significant physical and emotional toll, as a result of their PID diagnosis. Fear and apprehension were evident in concerns that their condition may suddenly worsen, or that they will be punished (through increased fatigue or illness) if they attempted to live their previous (now 'lost') 'normal' life. The participants also expressed guilt from having a diagnosis of PID, which directly or indirectly impacted their friends and family. Having to acknowledge these new limitations in their lifestyle was often expressed as feelings of anxiety or depression. Chronic illness often requires ongoing adaptation from the individual who is diagnosed, as well as adaptation by the individual's family/caregiver (Dobbie and Mellor, 2008).

The decline found for both groups in the SF-36v2, Role Physical score, over the course of the study, indicated greater limitations in their ability to perform work and/or physical activities,

as compared to population norms. This finding is consistent with research that has established correlations between chronic disease and reduced work productivity (Collins et al., 2005; Goetzel et al., 2004; Koolhaas et al., 2013). The participants in the exercise group had a slightly greater decline in the Role Physical score of the SF-36v2, which may represent the challenges in completing the exercise intervention reported by many during the interviews and journal entries. Research involving the chronic fatigue syndrome patient population is conflicting; some studies report a worsening of physical symptoms and fatigue with exercise (Yoshiuchi et al., 2007), while others suggest exercise does not have a negative impact (Loy et al., 2016). More research is needed to see if the findings from this study apply to the larger population of individuals with a diagnosis of PID.

In the interviews and journals, the participants often expressed feeling guilty about having to take time to rest or recover. They described how they feel about their friends and family not understanding their daily struggles, from both a physical and an emotional perspective. Social isolation was mentioned by many of the participants in the study. For some, this was due to their fatigue and inability to participate in activities beyond those required to function from day-to-day. For others, it was due to a fear of getting sick, and an attempt to avoid situations that might increase their exposure to germs or illness.

The slight decline in the SF-36v2, Role Emotional score for the exercise group indicated a trend towards a decline in mental health. It is possible that the participants in the exercise group experienced some emotional distress as they recognized their physical limitations while participating in the exercise intervention. The below average scores for both groups suggest that those with a diagnosis of PID have below average mental health and greater difficulty with work or other activities due to emotional problems, as compared to population norms. This is also

consistent with the results of the PSS-10 outcome measure, which investigated stress. Depression and anxiety are often seen in individuals with chronic medical conditions, especially in those with poor coping responses or limited social support (Turner and Kelly, 2000).

There was a hopelessness echoed by some of the participants; there was an understanding that they were diagnosed with a chronic disease that could not be cured, only managed. Even though most of the participants in the study were receiving treatment through IgG replacement therapy, some shared a despair over the permanence of their diagnosis; they explained that they felt broken and could not be 'fixed'. As one participant expressed, there was no magic supplement or solution to make her better. The participants also shared how the pharmacological treatment of IgG replacement can impact their QoL, both positively and negatively. The participants described negative side-effects and time requirements to complete their treatments, which often contributed to further social isolation and fatigue. This is also consistent with the literature, which notes that individuals with a chronic illness are especially vulnerable to social isolation due to a variety of physical and emotional factors (Holley, 2007).

Pain and lack of energy were also mentioned in the interviews and journals, with both groups demonstrating a decline in the SF-32v2, Bodily Pain score, indicating higher pain intensity impacting normal activities. Participants in the exercise group had a slightly greater decline, which may represent an increase in their reported bodily pain due to participation in the exercise intervention. For the SF-36v2, Vitality score, both groups indicated improved well-being, and more energy during the study period. The participants in the exercise group had a slightly greater improvement, which may represent a trend towards improved energy and well-being from participation in the exercise intervention. This finding is in contrast to the interview and journal entries, as well as the results of the FIS outcome measure, that showed greater

fatigue for the exercise group. The trend towards improvement on the SF-36v2 vitality score may have been secondary to the Hawthorne effect from participation in the study (McCambridge, Witton, and Elbourne, 2014). Despite this, both groups were well below average in the Vitality score, indicating that those with a diagnosis of PID have a below average feeling of well-being, with increased fatigue and exhaustion, as compared to population norms.

Participants shared how having to alter their lifestyle and cope with extreme fatigue often led to feelings of anxiety and depression. Many participants commented about having increased stress as they tried to navigate the healthcare system, insurance authorizations, and expensive treatments. They felt less able to cope with the stressors encountered, due to their fatigue and emotional state. There was a range of emotions expressed, with some relaying anger, resentment, and frustration over their diagnosis, while others focused on acceptance and healing. The concept of health-related hardiness has been used to explain the variation in adaptation to the stressors of chronic disease; health-related hardiness is linked to psychological, psychosocial, and physiologic adaptations (Brooks, 2003; Pollock, 1989).

There was also a devastating emotional impact shared by the participants when they lost a member of their acquired 'PID family' to disease complications, or to suicide, because of the emotional burden of the disease. This caused a profound emotional response in several of the participants. Research does link functional disability or physical illness to an increase risk for suicidal behavior (Fässberg, 2016). However, individuals with a chronic disease are at a higher risk for the development of a psychiatric disorder, most commonly depression or anxiety; the overlap of symptoms can make diagnosis even more challenging (Turner and Kelly, 2000). The slight decline in the SF-36v2, Mental Health score, for the exercise group indicated greater feelings of anxiety and depression. Again, it is possible that the participants in the exercise group

experienced some emotional distress as they recognized their physical limitations while participating in the exercise intervention. The below average scores for both groups suggest that those with a diagnosis of PID have greater feelings of anxiety and depression (consistent with the previously mentioned literature), with lower psychological well-being, as compared to population norms.

The control group was 0.05 short of meeting the MID for improvement in the Mental Component Summary (MCS) score. Despite this, both groups were well below average, implying that those with a diagnosis of PID have greater limitations in mental well-being, more frequent psychological distress, social and role impairments due to emotional issues, and poor overall health, as compared to population norms. Since the exercise group did have a decline in the MCS score, as compared to the control group, it is suggestive that participation in the exercise intervention had a negative impact on emotional health, perhaps due to the stress of a new activity. Participants in the exercise group had more frequent psychological distress, social and role impairment due to emotional issues, and a poorer overall health, at completion of the study period. This is supported through participant interviews and journals, with participant narratives expressing frustration, anxiety, and depression about an inability to engage in the exercise program at a desired level of intensity and frequency.

Many of the participants shared that the physical and emotional impact of their PID diagnosis impairs their ability to complete their activities of daily living. They described the need to ration their energy resources, and how their energy varied from day-to-day. The feeling of fatigue, lack of energy, and social isolation described by the participants is reflected by their perceptions of a reduced QoL. The slight improvement in the SF-36v2, Social Functioning scale for the exercise group, suggested improved engagement in normal social activities; this was

further substantiated through comments in the interviews and journals. Several participants in the exercise group mentioned finding an 'exercise buddy': meeting individuals while walking in a local park, or by becoming more active through exercise with a family member. This suggests that the exercise intervention has potential to lead to improved engagement in normal social activities. Research suggests that exercising with another person may lead to lower stress levels, but increase fatigue levels (Plante, Coscarelli, and Ford, 2001). The below average scores for both groups in the SF-36v2 for Social Functioning, as compared to population norms, suggest that those with a diagnosis of PID have a reduced engagement in social activities due to physical or emotional problems.

While fatigue has been explored and discussed in individuals with a diagnosis of PID, the issue of cognitive impairments, noted by almost every participant in this study, has not been explored, and is a novel finding in this study. Participants in this research study described a brain fog, which had a consistent characterization of symptoms. They described similar cognitive impairments of forgetfulness, word-finding deficits, and difficulty processing information. These symptoms are consistent with the descriptions of brain fog described in other immune system or inflammatory disorders, including cancer-related 'chemo brain' (Raffa, 2013), chronic fatigue syndrome (Ocon, 2013), and systemic lupus erythematosus (Mackay, 2015). Some participants attributed the brain fog to their fatigue, while others blamed their IgG replacement treatment. While this research study is not able to ascertain the cause of the cognitive impairment, there is a consistency and frequency that is likely linked to the PID diagnosis, disease process, and/or treatment. Only one participant did not experience this brain fog. Interestingly, he was the oldest participant in the study, however, he had also been practicing mindfulness, meditation, and cognitive behavioral therapy for the past three to four

years. Mindfulness training has been linked to improved attention and working memory (Brown, Goodman, Ryan, and Anālayo, 2016). Mindfulness-based stress reduction techniques have been shown to reduce cancer-related cognitive impairment (Johns et al., 2016), while meditation awareness training has helped to reduce the symptoms associated with fibromyalgia (Van Gordon, Shonin, Dunn, Garcia-Campayo and Griffiths, 2017).

In the theme centered on stigma and disease validation, many of the participants expressed their frustration at being told, "you don't look sick." They described the stigma associated with having a rare, chronic disease, where an individual may have a healthy external appearance, despite their disease having a significant physical and emotional impact. The emotions expressed in the interviews and journals included frustration, anger, fear, despondence, uncertainty, and isolation; these emotions are common for individuals with a rare disease going through the diagnostic process (Dudding-Byth, 2015). The participants often shared that getting their diagnosis of a PID was a relief. They had suffered from a variety of symptoms, often over several years, and were labeled as a "hypochondriac," as the "crazy" patient or, they were told they were "faking it," they were "lazy," and they should "toughen up." Being given these labels by healthcare professionals who they expected to treat and heal them, these participants expressed feeling greater stress, coupled with self-doubt and distress to their emotional well-being. Having a diagnosis validated the experience of having a chronic disease, which provided them with a sense of relief, despite the physical and emotional challenges experienced.

When the participants were asked to reflect on exercise, their participation in the exercise intervention, and the impact exercise has on their well-being and QoL, the common experience was that they wanted, and expected, the exercise to be beneficial. This was consistent with the high scores on the EBBS survey, where both groups indicated a higher perceived benefit from

engaging in exercise. Although they wanted to exercise, they described being too exhausted to participate consistently in an exercise program. They also expressed that exercise increased their level of fatigue, and that it did not seem to positively impact their PID. These perceptions are very similar to the rheumatoid arthritis (RA) patient population, who are often sedentary, but recognize that exercise has potential health benefits; for individuals with RA the key barriers to exercise were pain and fatigue, and exercise adherence could be increased through support from family, friends, and healthcare providers (Veldhuijzen van Zanten et al., 2015). Individuals with a diagnosis of chronic fatigue syndrome also recognize the health benefits of exercise, but reported exercise exacerbated their symptoms, and did not improve fatigue or HRQoL (Castro-Marrero, Sáez-Francàs, Santillo, and Alegre, 2017).

Based on the interviews and journal entries, the participants indicated the exercise intervention helped to motivate them, reduce their stress, decrease their social isolation, and direct their focus away from their disease. However, many participants also expressed a sense of frustration that they were not able to engage at a higher level of intensity, and that they felt forced, by their disease, to pace themselves by lowering their intensity and/or duration of exercise. Most participants did continue to experience fatigue during the exercise intervention, which often interfered with their ability to successfully complete their exercise goals.

Many of the participants in this research study were excited at the prospect of participating in an exercise intervention. They had a positive view of the benefit of exercise and were eager for an opportunity to feel healthy and to be, what they considered, ‘normal’. They acknowledged that exercise helped to reduce their stress, by giving them something to look forward to, and reduced their social isolation. However, they also emphasized that exercise only helped to reduce their stress when they were able to participate in an exercise regime.

Engagement in an exercise program helped participants recognize that they were still able to accomplish a physical activity (though at times this caused a negative impact, as it also made them face their physical limitations). Several participants reported they felt energized when they were exercising, although it also led to greater fatigue afterwards. Finding a good balance was challenging for many of the participants. The literature exploring fatigue in the PID patient population is extremely limited. The research surrounding exercise and fatigue in individuals with a diagnosis of chronic fatigue syndrome suggests use of a time-contingent approach to exercise that accounts for pacing and exasperation of fatigue symptoms, high frequency and low duration exercise with a slow ramp-up period, and an emphasis on aerobic exercises (Van Cauwenbergh, De Kooning, Ickmans and Kijs, 2012).

The Exercise Benefits/Barriers Scale (EBBS) was used to assess the perceived benefits and potential barriers to exercise at baseline and at the end of the eight-week study period. Higher scores on the EBBS are suggestive of a more positive perception about the benefits of exercise (Sechrist et al., 1987). For the EBBS, the control group showed a trend towards a greater perception about the benefits of exercise when comparing pre- to post-study data; in contrast, the exercise group indicated they had a lower perception of the benefits of exercise. This suggests that the participants in the exercise group may have recognized additional barriers to exercising; perhaps felt they were gaining less benefit from their participation in the exercise intervention. The perception of exercise being more of a detriment, by the exercise group, could be linked to the higher level of stress and increased fatigue.

The Self-Efficacy for Exercise Scale (SEE) was used to assess self-efficacy expectations relating to exercise participation. A higher score on the SEE suggests a greater degree of self-efficacy as it relates to exercise participation (Resnick & Jenkins, 2000). At the end of the study,

both groups demonstrated a decline in their SEE score, with the exercise group showing a greater decline. This suggests that the participants in the exercise group may have found the exercise intervention challenging to complete; the stress of a novel intervention may add to a decreased self-efficacy in the exercise group. This is linked to the participants explanation during the interviews and journal entries that they did not exercise at their desired degree of intensity or frequency, during the exercise intervention period.

The Subjective Exercise Experiences Scale (SEES) was used to assess the global psychological response to the experience of exercise. For the Psychological Well-Being (PWB) subscale, both groups demonstrated a slight decline in their PWB score, indicating they experienced a lower sense of positive well-being as it related to exercise at the end of the study period, regardless of their participation in the exercise intervention. The Psychological Distress Subscale (PD), demonstrated a slight increase in the PD score for both groups, indicating they both experienced an increase in psychological distress, as it related to exercise, regardless of their participation in the exercise intervention. For the Fatigue subscale, both groups demonstrated a slight decrease in their Fatigue subscale score, indicating they experienced a decrease in fatigue as it related to exercise, regardless of their participation in the exercise intervention. Using this scale, the decrease in fatigue can be interpreted as both positive and negative; it can represent less fatigue due to exercise (positive) or less fatigue because they are not exercising/active (negative). Based on the interviews and journal entries, this reduction in fatigue on the SEES is likely related to reduced engagement in the exercise intervention and reduced fatigue related to exercise; this measure of fatigue relates only to exercise, not to the overall fatigue that is measured through the FIS. While not statistically significant, analysis of the change scores from baseline to week two did approach significance for the exercise group (*p*

= 0.051). There was a temporary increase in the Fatigue subscale score during the second week of the study for the exercise intervention group; this suggests that participating in a novel exercise program resulted in more fatigue at that time point.

Using the SEES, both groups demonstrated a lower sense of positive well-being as it relates to exercise, regardless of their participation in the exercise program. The participants in both groups had small positive and negative vacillations over the course of the eight weeks, but no statistically significant findings. The SEES also indicated a trend towards an increased psychological distress as it related to exercise, regardless of participation in the exercise program. The participants in both groups had small positive and negative vacillations over the course of the eight weeks, but no statistically significant findings. These vacillations are representative of the episodic nature of a chronic disease condition, and the natural variability present in the disease symptoms (Vajravelu, O'Brien, Moll and Solomon, 2016).

Exercise resulted in feelings that were both positive and negative. Participants who struggled to complete the exercise program, due to fatigue or other barriers, reported a sense of discouragement and frustration. While they had hoped that an exercise program would help to improve their health and well-being, they found it often accentuated their physical limitations and fatigue. This resulted in greater emotional distress, which was expressed when the participants struggled to complete the exercise intervention. Fatigue was a commonly mentioned barrier, discussed by many of the participants, to completing the exercise intervention. A few participants had concerns that too much exercise would exacerbate their fatigue, pain, or illness. The concept of requiring adequate recovery time was an important point of discussion that remained at the forefront. Participants felt they needed more recovery time than expected; this is

an important consideration when designing an exercise program for individuals with a diagnosis of PID.

Infection Incidence and Non-Routine Medical Care

Because it has not been determined how exercise can affect individuals with a diagnosis of PID, it was important to investigate whether an exercise program would result in an increase in the infection incidence or need for non-routine medical care. Participants were asked to recall the number of infections and the number of non-routine medical visits to a variety of settings, and medical providers, in the eight-weeks prior to the study period. While these recall periods may be considered unreliable by many, the PID patient population is more likely to track infections and medical appointments due to continued requirement to validate their need for IgG replacement to insurance providers. Participants in this study were also asked to keep a record of infections and non-routine medical appointments during the eight-week study period. No statistically significant differences were found between the two groups for any of the outcome measures. This can be considered a favorable outcome, as it indicates that the participants in the exercise group did not develop an increased number of infections or an increased need for non-routine medical care, as compared to the control group, while they engaged in the exercise intervention. This is consistent with the literature that a low or moderate intensity exercise program will not have a negative impact on immune function (Bøyum et al., 1996; Fleshner, 2000; Romeo et al., 2010; Gillum et al., 2011), and especially important that this is also the case in an immune-compromised patient population. While this is a small number of participants, it provides healthcare providers with a foundation for the recommendation of an exercise program; knowing that exercise is not likely to increase infection risk or result in higher utilization of healthcare resources is critically important.

Development of a Conceptual Framework

Based on the results from the surveys, interviews, and journal entries, a conceptual framework about the continuum of living with a PID, specifically, the evolution of a 'new normal', was developed. This framework represents the key messages from the findings that emerged during this research study; the conceptual framework for dynamics of living with a diagnosis of PID is illustrated in Figure 13. The central concept is the individual's journey to re-define their identity following their diagnosis of a chronic disease. The participant interviews and journals, supported by qualitative outcomes, contained rich narratives that emphasized the struggle of these participants to define who they are following their diagnosis of a chronic disease. Identity was a key concern with the participants in the study; many conveyed their distress over the loss of self and the changes they identified in themselves as they adapted to a new lifestyle, directly linked with their diagnosis.

Many internal and external factors help influence an individual's physical and emotional well-being. Internal factors, such as coping skills, resilience, and perseverance are important in determining the internal response to a chronic health condition. Support systems, healthcare access, and the need for life-long treatments are just some of the external factors that can also influence an individual's response to a chronic health condition (Gallant, 2003; Turner and Kelly, 2000; Osborn, Moulds, Squires, Doty, and Anderson, 2014; Jones, Vogt, Chambers, Clowes, and Shrimpton, 2018). These factors combine to influence the individual's physical and emotional well-being. Along the continuum of their disease, there may be changes in those internal and external factors; these changes can alter the individual's well-being at any time along the span of living with their condition (Gallant, 2003; Turner and Kelly, 2000). This forms a foundation that determines whether an individual will develop a positive adaptation or a

negative adaptation to their chronic disease diagnosis (Pierobon, Giardini, Callegari and Majani, 2011; Sharpe and Curran, 2006; Brooks, 2003; Nicholas, 1993). Those that have a positive adaptation are more apt to embrace their 'new normal', demonstrate healthy coping behaviors, and have good physical and emotional well-being. Those who have a negative adaptation may be more likely to display anger, frustration, and hostility towards their 'new normal', demonstrating an inability to cope, and contributing to poor physical and emotional well-being.

The concepts of stigma and validation, two key concepts discussed by the participants in this study, can also influence the adaptation of the individual to their chronic health condition (Joachim and Acorn, 2000). Those who face constant stigma (as expressed by the participants: "you don't look sick" or "you're just being lazy") will find the scales tip towards negative adaptation; they are forced to overcome this negative perception about themselves. On the other side of the scale, is validation. Those who have their chronic condition validated by healthcare professionals, family, and friends, feel supported and understood (as expressed by the participants: "I'm not crazy, it's not all in my head" or "I'm not a hypochondriac"). The individuals in this study living with a diagnosis of PID, and perhaps other chronic health conditions, have expressed their experiences as a dynamic continuum.

This is not a fixed model that remains static over the course of their chronic disease. The scales may be tipped in one direction or the other at any time; loss of health insurance or a serious infection are just two examples that could tip the scale towards a negative adaptation. However, the individuals support system and resilience could serve to balance the movement in the scale (Folkman and Greer, 2000). The framework for living with PID, presented in Figure 13, is highly dynamic, with numerous factors that can influence the critical balance needed to promote a stable and realistic adaptation to the chronicity of their disease.

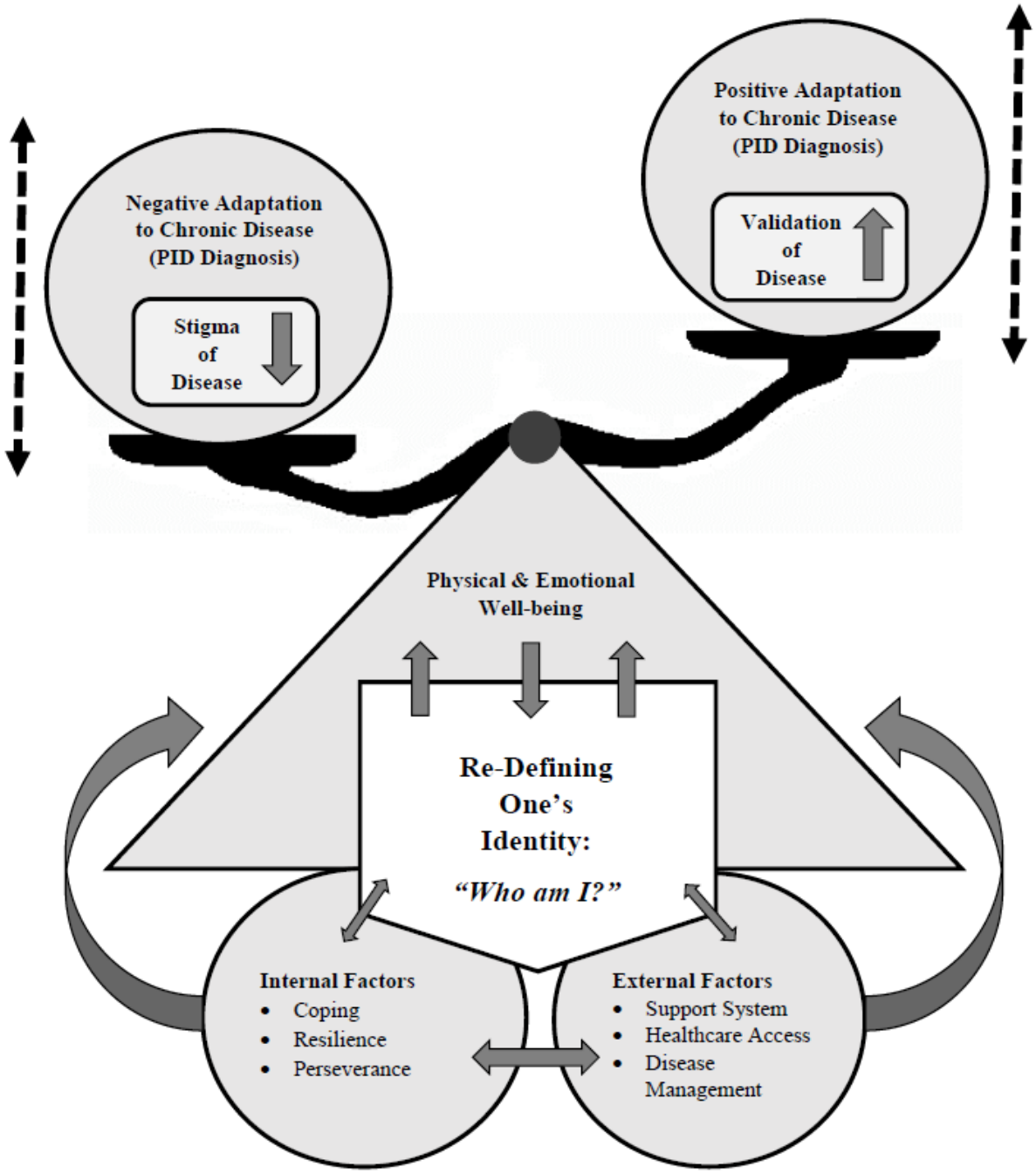


Figure 13. The Continuum of Living with PID: Evolution of a 'New Normal'

Implications

This research study provides a depth of foundational information about the impact of low to moderate intensity exercise on stress, fatigue, and QoL for individuals diagnosed with PID. Despite the lack of statistical significance derived from the quantitative data, there were noticeable trends that provide interesting observations about stress, fatigue, QoL, and exercise for individuals with a diagnosis of PID that were supported by rich, thick narratives of the qualitative themes generated.

It is important to note the trend in all domains of the SF-36v2, a valid and reliable measure used to assess QoL. All participants in this study, regardless of group, had scores that were below the 2009 population-based U.S. norms. The scores for the General Health domain, which measures general health status, was well below the population-based norms, and well below all other domains, for all participants and at both time points in the study. Additionally, the control group demonstrated a clinically significant decline, as compared to the established MID value, in the Physical Component Summary domain of the SF-36v2 during the eight-week study period. A lower score on this domain indicates greater limitations in physical functioning, higher levels of pain, and greater restrictions in participation in normal activities due to physical impairments, as compared to population norms. The exercise group did not experience this decline, suggesting that the exercise intervention had clinical benefits for this population, as it relates to the Physical Component Summary domain. Further research to determine if this is a real trend, or a random finding (since the outcome measures are of a single snapshot in time), would be necessary.

The lack of statistical significance found regarding infection incidence and non-routine medical visits can be interpreted as a positive finding. Having no difference between the two

groups indicates that a low to moderate intensity exercise program did not increase infection incidence or need for non-routine medical care for these participants. This finding can provide healthcare providers with increased confidence to prescribe a low to moderate intensity exercise intervention for an individual with a diagnosis of PID, without fear that it will increase their infection susceptibility.

While not statistically significant, the data trends also suggested that the exercise group had more fatigue and stress as compared to the control group. The trends noted in the outcome measures used in this study can help healthcare practitioners understand that individuals with a PID diagnosis have a much lower perception about their QoL, especially their overall health status, regardless of their participation in an exercise program. Healthcare providers need to be aware of the reduced perception of QoL, and the potential physical and emotional impact of exercise for this patient population. It may be of benefit for healthcare providers to directly address the concept of QoL with their patient and explore resources that might help improve this aspect of the patient's overall health and well-being.

The qualitative data provides valuable perspectives from those living with a diagnosis of a PID. This perspective enables healthcare providers to have a better understanding of the physical and emotional impact on those living with a rare, chronic disease. Validation of the symptoms and struggle was important to these participants; this is critical for a healthcare professional to understand when they are working with a patient with a diagnosis of PID. The participants in this study expressed feeling a stigma related to having an invisible illness, such as PID. This stigma can leave patients with an uncertainty about how much information to disclose regarding their medical condition, and often results in deliberate concealment in order to appear 'normal' (Joachim & Acorn, 2000a).

Normalization is the most common management strategy for patients with an invisible illness (Joachim & Acorn, 2000b); normalization was clearly evident throughout this study, as patients repeatedly discussed their desire to "just be normal." Engebretson (2013) found that stigmatization due to a chronic disease can result in internalization of the stereotype by the patient, isolation, reduced social status, and discrimination. These were all issues expressed by participants in the interviews and journals, who often worried that other people saw them as sick, lazy, or withdrawn. They spoke about their social isolation from friends and family and their inability to consistently attend gatherings or events. Participants also spoke about discrimination from friends, family, and healthcare providers; they often heard, "but you don't look sick" and were accused of being hypochondriacs.

The participants in this study were challenged to adapt to a 'new normal' by having to adjust their lifestyle. Many participants struggled with defining who they were, especially in the face of a chronic medical condition. They felt socially isolated, had overwhelming fatigue, elevated stress levels, and a decreased QoL. It is important for healthcare providers to understand the degree of emotional impact experienced by individuals with a diagnosis of PID, and to provide adequate support and resources, such as counseling, support groups, and referrals to other healthcare or holistic health providers.

A key concept that emerged from the journals and interviews, was the need to listen to, and hear, these individuals. They are acutely aware of their body, physically and emotionally, and healthcare professionals need to respect their patient's perspectives. It is this perspective, which informs the patient's reality. If they are feeling extreme fatigue, that is not for a healthcare professional to judge, excuse, or dismiss. What their healthcare professional perceives they should be able to accomplish, with regard to exercise or daily activities, may not

always be a realistic standard. While some individuals with a diagnosis of PID may need to be reassured or be encouraged more than others, the perceived limitations and barriers are still very real to each individual; these perceived limitations and barriers should be discussed through motivational interviewing techniques (Sohl, Birdee, and Elam, 2016).

Healthcare professionals need to understand the physical and emotional impact experienced by individuals with a diagnosis of a PID. Support and resources to address emotional well-being should be incorporated into the plan of care, and healthcare professionals should educate their patients diagnosed with a PID about coping strategies, stress management, and energy conservation. Dobbie & Mellor (2008) found that cognitive behavioral therapy may help reduce anxiety associated with chronic illness, while semi-structured support groups can help patients and caregivers better cope with a chronic medical condition. Expanded community, family, and patient education is paramount.

The interviews and journals also provided a better understanding of participants' perspectives about exercise. Exercise provided motivation and inspiration, but when the participants were not able to keep up with the exercise routine, they became frustrated and discouraged. Fatigue was a common limitation of participation in the exercise program; increased levels of fatigue was a common side-effect for those who were able to engage in the intervention. This is important to understand when developing an exercise prescription for individuals with a diagnosis of PID.

A baseline level of fitness is very important to establish when designing the exercise program. Heart-rate monitoring, VO_{2max}, or other objective measures of energy expenditure should be implemented to ensure consistency and prevent over-exertion. A perceived exertion scale may not provide an accurate assessment of energy expended in this patient population; the

perceived exertion may be dependent on whether the individual is having a good or bad day, even when assessing the same duration and intensity of exercise. The results of this study, while not statistically significant, showed a trend towards the exercise group having higher stress, more fatigue, and poorer emotional well-being compared to the control group. This contradicts most exercise-based health studies that promote improved physical and emotional health (Centers for Disease Control, 2011), even in populations that are immune-compromised (Sharif et al., 2018). However, the results for similar chronic, invisible illnesses such as fibromyalgia and chronic fatigue syndrome, which shows increased fear of movement and avoidance behaviors towards physical activities (Nijs et al., 2013). Short duration exercise programs, designed to minimize post-exercise fatigue, are important. In addition, frequent rest periods need to be incorporated into the exercise program design; again, this will help to minimize fatigue from over-exertion (O'Connor, 2017).

While the participants in this study recognized the benefits of exercise for their overall health, they feared that exercise would increase their fatigue and they perceived that exercise would not directly improve their chronic medical condition. This is important to understand, as the perceived effectiveness of exercise is one aspect that contributes to exercise adherence. Campbell et al. (2001) identified several other key factors that help determine exercise adherence, including: attitude towards exercise, perceived severity of symptoms, ideas related to cause of disease, and perceived effectiveness of exercise. In addition, an increased awareness of physical limitations may result in a profound impact on emotional well-being. This can be seen in patients with chronic obstructive pulmonary disease (COPD), where high anxiety correlates with poor exercise performance and reduced QoL (Giardino et al., 2010).

An important aspect of education for individuals with a diagnosis of PID are the concepts of pacing and goal-setting. Throughout this study, many participants expressed the idea of good days and bad days. These days ranged from not being able to get out of bed or take a shower, to feeling 'normal' and trying to make up for the bad days. On the good days, they expressed a tendency to do as much as they could, because they were not sure when another burst of energy would come. Because of this, they often over-exerted themselves, which resulted in several bad days. These individuals must learn how to best utilize their energy supply, which may vary day-by-day, to complete critical activities. Healthcare providers need to provide education to help these individuals better balance their energy expenditure and prevent over-exertion.

Education relating to goal-setting is another critically important topic from which this group of individuals would benefit. Learning how to establish and adjust goals applies to both an exercise program and their daily activities. One concept expressed by many participants was the frustration they experienced when they did not reach their exercise goal. Often, many participants set unrealistic goals when it came to exercise, given their baseline activity level and their past history with consistent participation in an exercise program. Kangovi et al. (2017) found that most patients have an awareness of areas they need to improve, that patients and providers tend to set goals that are overly ambitious, and that a higher self-efficacy for goal achievement is found early on (this self-efficacy will diminish without positive feedback). Based on the qualitative interviews, it was evident that the participants in this study were aware of the value of exercise and were motivated to exercise. Participants also expressed frustration when they were unable to achieve their self-directed exercise goals. Finally, most participants began the study highly motivated to engage in an exercise program; those who were able to see small improvements in their exercise ability and endurance were able to remain engaged and

compliant, while those who did not achieve their initial exercise program goals struggled to stay engaged.

In addition to teaching individuals with a diagnosis of PID how to set realistic and appropriate goals, they also need to learn how and when to modify their goals. Unexpected illnesses or infections, changes in their energy levels, and alterations in their emotional well-being may require goal modification. Participants with a chronic medical condition need to understand they can modify goals when appropriate. Goals need to be patient-directed, collaborative, and holistic (Tinetti, Naik & Dodson, 2016). It may be useful to utilize outcome measures, such as the Goal Attainment Scaling Measure or the Self-Identified Goals Assessment, to evaluate goal setting, planning, and appraisal phases (Stevens et al., 2013). Health coaching may need to be included by healthcare providers in the plan of care, to maximize QoL and well-being (Boehmer et al., 2016).

Since many individuals with a diagnosis of PID expressed difficulty in finding the energy to complete basic activities, and fewer participate consistently in an exercise program, there should be education about incorporation of exercise into their daily routine. Since fatigue and lack of energy were the most common barriers to completing the necessary exercise program, individuals with a diagnosis of PID may find incorporating small increments of increased activity into their daily routine to be more tolerable. These suggestions might include: climbing the stairs, instead of an elevator; parking at the end of the lot, instead of close to the store; or walking or jogging to the mailbox, instead of picking up mail when driving into the driveway. While these alterations in activity may not be viewed as a formal exercise program, this may be a good starting point, especially for those who are more sedentary or home-bound. Incorporating a healthier, more active lifestyle may be perceived by these individuals as requiring less energy

compared to a formal exercise program, making it easier to achieve a goal of increased activity. Many of the participants in this study expressed the challenge of having adequate energy levels to complete their necessary ADL and IADLs; further education and assistance may be required to help these individuals learn how to prioritize physical and emotional output.

Limitation and Delimitations

Limitations

The greatest challenge in this study was recruiting an adequate sample size, due to the rare nature of PID and participants being widespread throughout the country. Some participants were limited in their ability to complete the exercise intervention, while some participants did not complete the study (out of 36 enrollments, two dropped out after enrollment and prior to starting the study, while four dropped out during the study or were lost to follow-up). The Immune Deficiency Foundation (IDF) developed an extensive network of resources for patients with a diagnosis of a PID. A recent IDF initiated program, known as PI Connect, a Patient-Centered Outcomes Research Institute (PCORI) funded project, was available to connect patients and researchers (IDF, 2015). This newly established network, numerous social media networks, and the IDF 2017 National Conference were used to recruit participants for the study. Despite extensive recruitment, the desired sample size, 43 per group, was not achieved for this study. Having a small number of participants reduces the power of the study, and likely contributes to the lack of statistical significance in the quantitative data. The low sample size also contributes to an increased chance of a type II error.

A potentially high attrition rate due to the chronicity of the disease is often a concerning barrier for this type of research study; while there was a low attrition rate (11.1%) for this study,

it is likely due to the consistent weekly contact and extensive follow-up attempts made by the primary researcher with every participant. It would be challenging to complete the level of follow-up that was required for this group of participants, had the sample size been much larger.

While all the outcome measures selected for this study were shown to be valid and reliable measures, there may be variations in the responses that cannot be controlled. Outcome measures that ask participants about how they felt over the past four weeks can be impacted by the current emotional and physical status of the participants. While the participants were asked to take the pre- and post-study outcome measures at similar times of the day, and at a similar time in relation to their IgG replacement, there are many external factors than can also influence survey responses. These factors include fatigue, support system input (may be positive or negative), stress due to change in IgG product or health insurance, weather, and non-PID related stressors (which may also be positive or negative).

Despite providing participants with a clear expectation for exercise participation, some participants struggled to achieve the recommended 75 - 150 minutes of moderate intensity exercise, due to a variety of reasons. There was a lack of consistency among the participants when it came to completion of the recommended 75-150 minutes of moderate intensity exercise per week; some participants exercised much more than 150 minutes, some exceeded the moderate intensity level, while others did not meet the requested intensity or duration. Fatigue, lack of time, and weather conditions (in this case, there were extremely hot temperatures, as the study was conducted during the summer months) were key reasons participants struggled to complete the exercise program. Some participants struggled to complete the log of their exercises. Several participants would log their data days later, leading to potential for recall error in the exercises they tracked. Some participants did not keep an exercise log, and only

confirmed that they met the time and RPE requirements. Having the participants consistently complete their journals was another challenge. Despite specific and detailed instructions about the journal, several participants did not submit any journal entries. Others kept the journal in the beginning of the study, but stopped journaling partway through the eight-week period.

Individuals with a diagnosis of PID often suffer from other health conditions. Their ability to participate and engage in an exercise program, as well as their perception about their quality of life, may be impacted by medical conditions other than PID. This specific study was restricted in its ability to determine which medical condition was the most limiting for the individual participants. Two participants dropped out prior to the start of data collection due to medical reasons (unrelated to this study), one participant completed the initial baseline surveys and then dropped out due to a medical reason (also unrelated to this study). Three participants were lost to follow-up, for the one participant in the exercise group, it could not be determined if this was related to the intervention, or not.

There were more females participating in the study, though the distribution was similar across the two groups (the control group was comprised of 13 females and 3 males, while the exercise group was comprised of 16 females and 2 males). This does contribute to a potential bias of the data and limits its generalizability for males with a diagnosis of a PID. Additionally, the participants in the study were almost exclusively White/Caucasian (100.0%, n=16 for the control group and 88.9%, n=16 for the exercise group); again, this leads to bias and limits generalizability. The limited diversity found in this study does not match the normal variations in gender and ethnicity in the PID population, leading to potential bias of the results. However, the limited diversity could also be considered beneficial, because the group is more homogenous and there are less variations in the demographic factors to impact the results.

Delimitations

A high attrition rate was avoided by providing adequate support to the participants throughout the length of the study. This was accomplished through weekly follow-ups via email, and constant availability to address concerns with their exercise program (or normal activity levels). Participants randomized to the control group may have considered dropping out, due to a desire to participate in the exercise program. To prevent this, all participants in the control group were provided with access to the same semi-customized exercise program and tracking app for a minimum of eight weeks, following completion of their eight-week study period. Despite routine and repeated contact with all participants, a total of three participants were lost to follow-up and did not return their final surveys.

To encourage completion of the pre-study surveys, weekly surveys, and post-study surveys, multiple methods were employed. While the survey outcome measures were primarily available electronically, it was noted that not all participants were able to complete the surveys in electronic format. Participants were provided with the option of a paper survey (mailed to them and returned via pre-paid envelope), an electronic survey in either Word or fillable PDF format (to be returned via email attachment), or a Google Doc file (with a private link shared with the individual participant). All three methods were utilized in this study, were based on individual participant preference. Initially, there were minor issues with the fillable PDF form, which were discovered by the first participant. The researcher was able to correct these issues, prior to sending the forms to additional participants.

During the interviews and journaling, participants are sometimes reluctant to fully divulge their feelings and perceptions. By explaining to the participants that the researcher shares the diagnosis of a PID, participants were more willing to share their feelings about their

experience. Given that the researcher is diagnosed with a PID, the researcher may not be able to separate her own personal experiences from that of the participants; this could have potentially influenced the coding and development of themes in the qualitative data. By following an interpretive methodology, the researcher did not need to bracket and could contribute her own experience and perspectives in gaining an understanding of the phenomenon. However, to further ensure that there was no bias in the development of the themes, an external consultant was involved in reviewing the transcriptions and themes. The external consultant was a physical therapist with more than thirty years of experience as a professor of physical therapy; she had experience with qualitative research focusing on QoL and stress, but not in working with individuals with PID. To ensure further accuracy with the analysis of the transcriptions and the development of the themes, the committee chair of this thesis with extensive qualitative experience and limited knowledge of the population with PID, was also involved in the process of thematic review and analysis.

A professional academic transcription services was utilized to complete the transcriptions of the interviews. There were noted errors in the transcriptions of every post-study participant interview. To remedy these errors, and ensure that correct information was obtained, participants were sent copies of their transcripts for verification of accuracy. Several participants did make edits or revisions of their interview transcriptions. Additionally, all content from the transcriptions that was included in the qualitative analysis was verified by the researcher for accuracy, by comparing the transcript to the original audio recording.

There was potential for error to occur during the transfer of the survey outcome measures to the electronic forms. Errors can invalidate the reliability and validity of the outcome measures. Multiple reviews of the conversions were completed to prevent any transcription

errors from occurring in the survey data. Errors could also occur when transferring data from the completed surveys to the data analysis software. Again, review of the transcribed data was completed by the primary researcher to ensure accuracy.

There was potential bias in patient recruitment, as patients were primarily recruited through social media. limiting generalizability. While social media recruitment is one of the most cost effective and fastest way to recruit participants from a population with a rare disease, it can create bias, due to the most motivated respondents participating in the study. Young adults using social media are noted to be more extraverted, while older adults using social media are more open to new experiences (Correa, Hinsley & Gil de Zuniga, 2010). This more open, extraverted, and potentially motivated audience may contribute to bias in the results. Advertisement of the research study was shared on multiple social media sites for PID but may not have reached all individuals on those social media platforms.

Recommendations for Future Research

Future research about the impact of exercise on stress, fatigue, and QoL for individuals with a diagnosis of PID should include a larger sample size. A larger number of participants would increase the power, reduce the chance of a type II error, and increase the potential for statistical significance. There needs to be greater diversity of the participants, especially as it relates to gender and ethnicity. Future studies would also benefit by focusing on one diagnostic category of PID (such as only participants with a diagnosis of Common Variable Immune Deficiency), due to the significant variability of presentation for the different types of PID diseases (Picard et al., 2015). Since a diagnosis of PID can impact individuals of all ages, including participants under the age of 18 years would also provide a greater breadth and depth of understanding and generalizability of data obtained. Finally, the exclusion criteria of

participation in 75 minutes of structured exercise did eliminate a number of individuals from participating in this study; it would be beneficial to include those participants in future exercise-focused studies that examine type of exercise and exercise dosage.

Future research should incorporate a longer exercise intervention period of 12-16 weeks duration, to determine if the length of the exercise intervention has any impact on the results. This should also include a longitudinal follow-up to determine if exercise provides any long-term impact over six months to one year. Another important consideration for future studies, is to require participants to complete a more structured or regimented exercise program. In this study, participants were provided with flexibility in the exercise program, to encourage participation and engagement; they were able to participate in a wide variety of exercises, provided they met the required RPE and total exercise time per week. It would be especially helpful to know if a specific frequency, duration, or intensity of exercise is more beneficial than others. Future studies could also compare different types of exercise (aerobic, strength, flexibility, balance, aquatic) to determine if the type of exercise has any impact on the results. Use of fitness tracking devices or heartrate monitoring would be beneficial in quantifying the exercise that is completed by the participants.

This research study did not include pediatric participants, which makes up a large number of the PID patient population. A future study should include, or focus on, pediatric PID participants. This may prove to be more challenging when attempting to quantify the amount of exercise. Younger children may not be engaged in a standard exercise routine, but may be encouraged to participate in physical activity through sports or play on a routine basis. The use of fitness tracking devices might prove even more useful when studying this subset of the PID population, to more accurately quantify participant's physical activity level.

Future studies would also benefit from analysis of laboratory markers for stress and immune function. This research study relied on survey data and individual recall, which is subject to inaccuracy. Using laboratory values, such as blood or salivary cortisol (assuming the participants are not being treated with steroids), leukocyte counts, salivary IgA, quantitative IgG levels, lymphocyte counts, and natural killer cell counts, would all provide valuable data to compare to patient perception, provided through the survey outcome measures. The use of immune function markers must be carefully considered, due to normal fluctuations and those due to external influences. Cortisol can be influenced by the time of day and through the intake of corticosteroids, which some individuals with a diagnosis of PID are given prior to IVIG, or take on a regular basis for comorbid conditions. IgA measurements for those with an absence of IgA will not contribute any useful data. IgG will vary depending on the amount of IgG replacement product infused and the frequency of infusions; those with a weekly SCIG infusion have a steadier state, as compared to those on IVIG, who experience more notable peaks and troughs in their plasma IgG concentration (Berger, 2004). Given the limited research available on individuals with a diagnosis of PID, especially as it relates to exercise, there is much knowledge left to discover.

Finally, additional qualitative research should be done to better understand the experience of the physicians, and other healthcare professionals, as they provide care to individuals with a diagnosis of PID. It would be beneficial to understand the barriers, challenges, and resources available to those faced with diagnosing and treating these individuals. It would also be worthwhile to explore the experiences of family members and caretakers of individuals with a diagnosis of PID.

Conclusions

While the small sample size of this study influenced the ability to find statistical significance in the quantitative data, the interviews and journals provided an abundance of rich narratives about stress, fatigue, QoL, and exercise in the PID patient population. Healthcare professionals who treat individuals with a diagnosis of PID need to understand the challenges and barriers faced by these individuals as they attempt to participate in an exercise program.

A low to moderate intensity exercise program can be recommended to an individual with a diagnosis of a PID, without fear that it will increase the individual's susceptibility to infection or increase their need for non-routine medical care. These programs should still be monitored to assess the individual's response, especially when first starting a new exercise program. While there may be no negative physical impact from an exercise program, it is important to consider the impact exercise will have on the emotional well-being of the patient. Based on the findings of this study, it is important to consider the risk/benefit ratio to determine if the physical benefits will outweigh the potential harm to emotional well-being. The frequency and intensity of the exercise program must be carefully tailored to the individual patient. Additionally, there must be adequate flexibility within the program to accommodate for days when the patient is too fatigued to complete their exercises.

A conceptual framework about the continuum of living with PID, presented in Figure 13, serves to illustrate the continuum of this chronic disease. This framework highlights the primary theme of the loss of identity and re-defining a 'new normal'. It also emphasizes the numerous factors that can impact the individual and influence their physical and emotional well-being; this framework helps to illustrate the positive or negative adaptations that may occur with a chronic

health condition. It is critical to understand that those with a diagnosis of PID may move along the continuum, between negative and positive adaptation, at any time within the disease process.

Healthcare professionals should approach the treatment of individuals with a PID from a holistic, collaborative, and interprofessional approach, working with physicians, nurses, psychologists, counselors, social workers, care managers, occupational therapists, recreational therapists, nutritionists, and pharmacists, to provide a comprehensive wellness plan. Physical therapy programs need to expand their curriculum to provide a more comprehensive understanding of chronic disease. Academia needs to go beyond the understanding of the physiological condition and the optimal physical interventions. Physical therapy curriculum needs to incorporate a stronger foundation for understanding the emotional impact and the influence of psychosocial conditions for the patient with a chronic disease. Academic and clinical education needs to focus on specific rehabilitation interventions for coping, stress reduction, mindfulness, cognitive-behavioral therapy, energy conservation, pacing, imagery, and appreciation of the patient experience. As physical therapists, and movement specialists, it is important to understand that physical recovery is achieved through a biopsychosocial approach that is impacted by emotional recovery for individuals with a chronic health condition.

Appendix A

Clinical Trials Registration

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: July 3, 2017

ClinicalTrials.gov ID: [Not yet assigned]

Study Identification

Unique Protocol ID:	IRB00010183
Brief Title:	The Impact of Exercise on Stress, Fatigue, and Quality of Life in Individuals With Primary Immunodeficiency Disease.
Official Title:	The Impact of Exercise on Stress, Fatigue, and Quality of Life in Individuals With Primary Immunodeficiency Disease.
Secondary IDs:	IRB00002823 [Nova Southeastern University]

Study Status

Record Verification:	July 2017
Overall Status:	Recruiting
Study Start:	June 27, 2017 [Actual]
Primary Completion:	November 2017 [Anticipated]
Study Completion:	November 2017 [Anticipated]

Sponsor/Collaborators

Sponsor:	Stockton University
Responsible Party:	Principal Investigator Investigator: Kerri Sowers PT, DPT, NCS [ksowers] Official Title: Assistant Professor of Health Science Affiliation: Stockton University
Collaborators:	Nova Southeastern University

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: IRB00010183 Board Name: Stockton Univeristy IRB Board Affiliation: Stockton University Phone: 609-652-4484 Email: grants@stockton.edu Address:

	101 Vera King Farris Dr. Galloway, NJ 08205
Data Monitoring:	No
FDA Regulated Intervention:	No

Study Description

Brief Summary:	This aim of this research project is to determine if low to moderate level exercise can have an impact on stress, fatigue, and quality of life for individuals diagnosed with a primary immunodeficiency disease. This 8-week study will compare participants engaging in a semi-customized, home exercise program (exercise intervention group) to participants performing normal activities (non-exercise control group). This study will track stress, fatigue, and quality of life in individuals with a diagnosis of primary immunodeficiency disease, using standardized questionnaires, journals, and interviews.
Detailed Description:	This aim of this research project is to determine if low to moderate level exercise can have an impact on stress, fatigue, and quality of life for individuals diagnosed with a primary immunodeficiency disease. Many individuals diagnosed with primary immunodeficiency disease report chronic fatigue and/or pain, which can potentially limit their participation in exercise and physical activities. Research shows that regular exercise can improve both physical and mental health for individuals diagnosed with a chronic medical condition. Exercise is a healthy and low-cost alternative to some medications, and may be an effective addition to the treatment plan for many patients with primary immunodeficiency disease. Research also suggests that low level exercise may be beneficial to immune function, while intense, or prolonged exercise can be harmful. This 8-week study will compare participants engaging in a semi-customized, home exercise program (exercise intervention group) to participants performing normal activities (non-exercise control group). This study will track stress, fatigue, and quality of life, using standardized questionnaires, journals, and interviews. Weekly contact will be made with all participants throughout the 8 weeks of the study. Individuals in the exercise group will be asked to complete up to 150 minutes of exercise, per week, at the 11-14 rating of perceived exertion. Participants who are randomized to the control group will continue their normal activities; they will also be given the opportunity to participate in the exercise program at the end of the 8 week study. To help assess the safety of a low to moderate level exercise program for individuals with primary immunodeficiency disease, this research will track the number of infections, non-planned medical visits, or increased medication usage during the study (compared to 8 weeks prior to the intervention). This research will help provide valuable information about the safety and effectiveness of an exercise program for individuals with a primary immunodeficiency disease.

Conditions

Conditions:	Primary Immune Deficiency Disorder Common Variable Immunodeficiency Specific Antibody Deficiency Hypergammaglobulinemia
Keywords:	Exercise Stress Fatigue Quality of Life

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	No masking
Allocation:	Randomized
Enrollment:	100 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Exercise Group Participants will engage in up to 150 minutes of exercise per week, at a level of 11-14 on the Borg Rate of Perceived Exertion scale.	Exercise Program Participants will utilize the Physitrack exercise program to engage in up to 150 minutes of exercise at a rating of 11-14 on the Borg Rate of Perceived Exertion scale, per week.
No Intervention: Control Group Participants will continue normal activities, with no new participation in exercise program (may engage in less than 75 minutes of non-structured exercise per week).	

Outcome Measures

Primary Outcome Measure:

1. Short Form 36 version 2
   Measure of quality of life.

   [Time Frame: Pre-study and post-study]
2. Fatigue Impact Scale
   Measure of fatigue.

   [Time Frame: Pre-study and post-study]
3. Exercise Benefits/Barriers Scale
   Measure of perceptions about exercise.

   [Time Frame: Pre-study and post-study]
4. Perceived Stress Scale 10
   Measure of stress.

   [Time Frame: Pre-study and post-study]
5. Self-efficacy for Exercise Scale
   Measure about ability to comply with exercise program

   [Time Frame: Pre-study and post-study]
6. Subjective Exercise Experience Scale
   Measures perceptions about participation in an exercise program

   [Time Frame: Pre-study, weekly, post-study]

Secondary Outcome Measure:

7. Infection Incidence
   Measure of number of infections that have occurred

   [Time Frame: 8 weeks prior to the start of study, and the 8 weeks during the study]

8. Unplanned use of medical provider
   Number of unplanned visits to a medical provider

   [Time Frame: 8 weeks prior to the start of the study, and the 8 weeks during the study.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Sex:	All
Gender Based:	No
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

- 18 years of age or older.
- Physician diagnosis of a primary immunodeficiency disease (as evidenced by physician letter or medical documentation/report)
- Willingness to participate in eight-week exercise program

Exclusion Criteria:

- Current participation in a structured exercise program for greater than 75 minutes per week
- Any medical condition that prevents participation in a low to moderate level exercise program (such as, but not limited to, uncontrolled asthma, unstable cardiac condition, acute orthopedic injury which requires restricted activities)

Contacts/Locations

Central Contact Person: Kerri Sowers, PT, DPT, NCS
Telephone: 609-652-4418
Email: Kerri.Sowers@stockton.edu

Central Contact Backup:

Study Officials: Kerri Sowers, PT, DPT, NCS
Study Principal Investigator
Stockton University

Locations: United States, New Jersey
Stockton University
[Recruiting]
Galloway, New Jersey, United States, 08205
Contact: Kerri Sowers, PT, DPT, NCS 609-652-4418
Kerri.Sowers@stockton.edu
Sub-Investigator: Bini Litwin, PhD, MBA
Sub-Investigator: Alan Lee, PhD CWS GCS
Sub-Investigator: Mary Lou Galantino, PhD, MSCE

IPDSharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information:

Appendix B

Informed Consent and Protected Health Information Release

STOCKTON UNIVERSITY

School of Health Sciences

P: 609.652.4501 • F: 609.652.4858

101 Vera King Farris Drive | Galloway NJ 08205-9441
stockton.edu

Informed Consent Form

For participation in the Research Study: ***The impact of exercise on stress, fatigue, and quality of life in individuals with Primary Immunodeficiency Disease.***

Funding Source: None

IRB protocol #: IRB00010183 (Stockton University) and IRB00002823 (NSU).

For questions/concerns about your research rights, contact:
If you have any questions about this research study or your rights as a research subject, you can contact the principle investigator, Dr. Kerri Sowers by email. Kerri.Sowers@stockton.edu or by phone, (609)652-4418
Institutional Review Board, Stockton University, (609) 652-4844; *grants@stockton.edu*
Human Research Oversight Board, Nova Southeastern University, (954) 262-5369, Toll Free: (866)499-0790, IRB@nsu.nova.edu

Why am I being asked to volunteer?

You are being invited to participate in this research study as an individual with a diagnosis of a Primary Immunodeficiency (PIDD). You must be 18 years, or older, to participate. This study will be asking some participants to engage in an eight-week exercise program, and some to continue their normal activity level. Information will be collected about your stress levels, fatigue levels, and quality of life, through questionnaires, journal entries, and interviews. Your participation is completely voluntary, meaning it is your decision to participate, or not. You will need to carefully read this form to learn about the study, and the potential risks or benefits. The principle investigator will also explain the purpose and plan of the study to you prior to you giving your consent to participate. If you have any questions about this study, please ask the principle investigator. If you choose to participate in the study, you will need to initial and sign this form. Your consent includes allowing audio recording of a one-on-one interview with the principle investigator, which will be done at the end of the study period.

What is the Purpose of the Study? The primary objective for this research study is to assess the impact of participation in a low to moderate level, semi-customized, home-based exercise program on stress, fatigue, and quality of life. Participants will be randomized to the eight-week exercise program, or to the control group, where you will continue your normal activities. If you are randomized to the control group, you will be given the opportunity to participate in the eight-

week exercise program, at the end of the study. The study will also track the number of infections, non-planned medical appointments, and changes in relevant medications, to help determine the safety of exercise for individuals with PIDD.

To be included in this study, you must meet the following criteria:

- 18 years of age, or older
- Physician diagnosis of PIDD
- Willingness to participate in an eight-week exercise program
- Able to read, understand and speak English.

If you meet any of the following criteria, you are **not** eligible to participate in this study:

- Currently participating in a structured exercise program for more than 75 minutes per week
- Any medical condition that prevents or limits participation in a low to moderate exercise program (such as, but not limited to: uncontrolled asthma, unstable cardiac condition, and/or acute orthopedic injury which restricts activity)

What will I be doing, if I agree to participate? Once you agree to participate in this study, some basic information will be collected by the principle investigator. This will include information such as age, time since diagnosis, specific diagnosis (type of PIDD), current treatment (route of administration, dosage amount, and frequency of dosage), gender, ethnicity, employment status, type of health insurance, and income. All participants will be asked to recall infection incidence and non-planned medical intervention in the prior 8-week period. Information collected will include: number of infections, and the number and type of non-planned medical appointments related to PIDD. You will be randomly assigned to the exercise group or control (normal activities) group. Participants in the exercise group will engage in an eight-week, semi-customized, home-based, low to moderate level exercise program. All participants will complete questionnaires before and after the eight-week period. All participants will complete a weekly questionnaire, and 1-2 journal entries per week. A one-on-one interview (which will be audio recorded), with the principle investigator, will be completed at the end of the study period.

Is there any audio recording?

This research project will include audio recording of the individual interview with the principle investigator at the end of the study. The interview will include questions about your experience during the study period, as it relates to stress, fatigue, and quality of life. The audio recording will be done using computer software and a handheld audio recording device. This audio recording will be available to be heard by the principle investigator, the dissertation chair and committee members. The recording will be kept secure in an encrypted file, in a locked drawer, in a locked office of the principle investigator). The recording will be kept for 7 years after completion of the research study; it will be destroyed after that time according to federal and state regulations, through deletion of files and reformatting of the encrypted flash drive. Because your voice will be potentially identifiable by anyone who hears the recording, your

confidentiality for things you say on the recording cannot be absolutely guaranteed, although the researcher will try to limit access to the recording as described in this paragraph.

What are the dangers to me? There are inherent risks involved when participating in an exercise program. The risks associated with this study are no greater than the risks you normally assume when exercising on your own. The home exercise software program will provide written and video instructions on how to safely perform the exercises. Should you sustain an injury or illness related to the exercise program, there is no compensation or medical treatment provided by the researchers or organizations linked to this study. The risks associated with the audio recording of your interview are discussed above. Your interview and journal entries may pose emotional risk, as you are required to disclose your feelings about your personal experiences relating to stress, fatigue, quality of life, exercise and your diagnosis of PIDD. Should you have any questions or concerns, or sustain a research-related injury or illness, you must contact the principle investigator, immediately, at the numbers listed at the beginning of the form. You may also contact the IRB, at either Stockton University or Nova Southeastern University, with related questions or concerns about this study, at the numbers listed at the beginning of the form.

Are there benefits for participation? You will also have access to a semi-customized home-based exercise program designed for you by the principle investigator for a period of 8 weeks. Participants who are randomized to the control group will be provided with access to the eight-week home exercise program at the completion of the study.

Is there any cost to me? Will I be paid to participate? There is no cost to participate in this study. There is no fee to you to access the PhysioTrack home exercise software program. The exercise program can be completed in your own home and can be done without specialized equipment. You will not be paid to participate.

How will you keep my information private?

Your privacy is very important and every effort will be made to protect your information.

1. Personal information and health information, to be collected in the study, was mentioned previously, in the section related to procedures.
2. Your information is critical to understanding the data collected in this study. To protect this information, your personal information will be identified through a number. The audio recording will not identify your name; the transcription of the audio interview will be identified by the numeric code. The code for this key will only be available to the principle investigator. In addition, this key will be kept in a locked file, in a locked office, of the principle investigator. This information will be destroyed 7 years, according to federal and state regulations, after the study is completed.
3. The only individuals or organizations who may access your personal information and health information are the principle investigator, their dissertation chair and committee, and the IRBs.
4. All information obtained in this study is strictly confidential unless disclosure is required by law.

5. Your information will not be used, or disclosed, for research not related to the purpose of this study.
6. The results from this study will not become part of your medical record.
7. You will be able to request access to your personal information, and collected data, once the study is complete.

What if I do not want to participate or I want to leave the study? You can choose not to participate in this study at any time. You may also choose to withdraw from the study at any time, with no penalty. To leave the study, you only need to inform the principle investigator in writing. There is no penalty for choosing to leave or not participate. If you choose to withdraw from the study, the data collected **before** the date you leave will be used as part of the research, and kept for 7 years from the conclusion of the study.

Other Considerations

If significant new information pertaining to the study becomes available, which may relate to your willingness to continue to participate, this information will be provided to you by the principle investigator.

Voluntary Consent by Participant

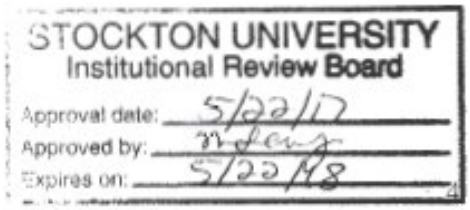
By signing this form, you agree that you:

- Have been told the reason for the study.
- Have had all your questions about the study have been answered.
- Have read and understand this form (or someone has read and explained it to you).
- Will answer all questions honestly.
- Will comply with the study procedures, as best you can.
- Have been told that you may ask the researchers any study-related questions in the future or contact them in the event of a research-related injury.
- Have been told that you may ask Institutional Review Board (IRB) personnel questions about your study rights.
- Are entitled to a copy of this form, after you have read and signed it.
- Voluntarily agree to participate in the study entitled: **The impact of exercise on stress, fatigue, and quality of life in individuals with Primary Immunodeficiency Disease.**

I have read this consent form and understand all of the above.

Signature of the Participant:_____ Date:_____

Signature of Witness:_____ Date:_____



Initials_____ Date_____

Nova Southeastern University

Authorization for Use and Disclosure of Protected Health Information in Research

Section I.

Sponsor, if applicable: N/A

Title of the Study: The impact of exercise on stress, fatigue, and quality of life in individuals with Primary Immunodeficiency Disease.

Study Number: _____

NSU IRB Protocol Number: _00002823____Stockton IRB:_00010183_____

Name of Principal Investigator: Kerri Sowers PT, DPT, NCS

Participant's Name:_____

General Information

In order for you to participate in this study, you must authorize the researchers to access and/ or obtain and/or use some of your personal health information. Medical treatment will not be conditioned on signing this authorization, unless the treatment is related to the research study described above.

This form describes what health information about you will be collected during this study and who may use, disclose and receive your health information.
signing this form, you agree that designated health information may be used and disclosed during this study. We will only collect information that is needed for the study. Your health information will only be used and given out as explained in this Authorization form or as permitted by

- ✓ You have the right to inspect or copy your protected health information to be used or disclosed as permitted under federal law (or state law to the extent the state law provides greater access rights).

Please read the information carefully. Please feel free to ask questions about this Authorization, Nova Southeastern University's ("NSU's") Notice of Privacy Practices, or the study before signing this form.

Section II. Uses and Disclosures Covered By This Authorization

A. I hereby authorize:

- ✓ The Principle Investigator and Dissertation Committee members (through Nova Southeastern University and Stockton University)

to use or disclose the following protected health information ("PHI"):

- ✓ Medical treatment and related information, including: medical diagnosis relating to Primary Immunodeficiency Disease (PIDD), information from laboratory and diagnostic tests (relating to PIDD), self-reported medical history (relating to PIDD treatment and infection incidence), salivary IgA, salivary cortisol, and other tests or medical procedures performed as part of this research study.
- ✓ Protected Health Information learned during telephone calls, surveys, questionnaires and journal entries done as part of this research study

B. Who may use, share and receive your health information as part of this study

During the study, the investigators and other authorized individuals involved in the study at Nova Southeastern University and Stockton University will see your self-reported health information and may give out your health information to the persons or entities listed in section C. These individuals include the research investigator and the research staff, the human research oversight board (Institutional Review Board or IRB) and its staff, legal counsel, research office, compliance office, administrators of the organization and other people who need to see the information in order to conduct the research study or make sure it is being done properly.

C. Additional Individuals and Entities who may use, share, and receive your protected health information.

Your health information may also be shared with federal and state agencies that have oversight of the study or to whom access is required under the law. These may include: **None**

The information collected in this research study will not be included as part of your medical record. Your insurance company will not be contacted by the researchers as part of this research study.

The following researchers, companies and/or organization(s) outside of Nova Southeastern University may also use, share and receive your health information in connection with this study:

- Weloty Academic Transcription Services will be used to transcribe the audio-recording from your interview; your personal identity and health information will be confidential, and not disclosed to Weloty Academic Transcription Services.

D. Purpose of the use and disclosure of health information

The reason we are asking for your permission to use and disclose your protected health information is, for example, to allow the University, regulatory agencies, and study sponsors to assess and/or assure compliance with the study protocol, to evaluate the effectiveness of the study, and/or to provide protection to you as a research study participant. The disclosure and use of your information will continue after your participation in the study has ended. There is no expiration date for the use of your health care records from the study. Any information about you disclosed to the individuals/entities identified above may be re-disclosed by them; however, such re-disclosure is not under the protections of this Authorization and may no longer be protected by state or federal law.

The Sponsor and its agents may disclose your health information to each other and use it for the purposes of monitoring the study, future research, the development of scientific databases and the development of new products. The Sponsor and its agents may also disclose your health information to the FDA and other regulatory agencies as necessary to report information regarding the safety and effectiveness of any study product or device that is the subject of this Study.

Even if the terms of the consent say otherwise, this Authorization does not expire, unless you revoke your Authorization in writing.

* * * * * * * *

I have read the above information provided and I am providing my authorization for the use and disclosure of health information as described above.

I understand that I have the right to revoke this authorization, in writing, at any time without penalty or loss of benefits to which I am otherwise entitled, or without jeopardizing my medical care unrelated to the study provided by my health care provider by sending written notification to:

Kerri Sowers PT, DPT, NSC

Stockton University

101 Vera King Farris Dr., Galloway, NJ 08215

I understand that I may also revoke this authorization through the procedure described in NSU's Notice of Privacy Practices. I understand that a revocation is not effective to the extent that those listed on this form including but not limited to the covered entity, researcher, research sponsor or affiliated companies has relied on the authorization for the use or disclosure of the protected health information.

I hereby acknowledge that I have read and understand the preceding Authorization form. All of my questions about this Authorization form have been answered to my satisfaction. By signing below, I permit **Kerri Sowers** and the others listed on this form to use and share my health information for this study. I will be given a copy of this signed form.

_____ _____

Signature of Participant or Personal Representative Date

_____ _____

Name of Participant or Personal Representative Participant Date of Birth

_____

Description of Personal Representative's Authority

NSU NOVA SOUTHEASTERN UNIVERSITY

HIPAA Notice of Privacy Practices

This notice describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

I. Uses and Disclosures of Protected Health Information

Nova Southeastern University (NSU) may use your protected health information for purposes of providing treatment, obtaining payment for treatment, and conducting health care operations. Your protected health information may be used or disclosed only for these purposes unless NSU has obtained your authorization or the use or disclosure is otherwise permitted by the HIPAA Privacy Regulations or State law. Disclosures of your protected health information for the purposes described in this Notice may be made in writing, orally, or by facsimile. Communications to you may be made by mail, facsimile, or by telephone. For example, NSU may communicate to you by leaving messages on your answering machine.

A. Treatment. We will use and disclose your protected health information to provide, coordinate, or manage your health care and any related services. This includes the coordination or management of your health care with a third party for treatment purposes. For example, we may disclose your protected health information to a pharmacy to fulfill a prescription, to a laboratory to order a blood test, or to a home health agency that is providing care in your home. We may also disclose protected health information to other physicians who may be treating you or consulting with your physician with respect to your care. In some cases, we may also disclose your protected health information to an outside treatment provider for purposes of the treatment activities of the other provider.

B. Payment. Your protected health information will be used, as needed, to bill and collect payment for your health care services. This may include certain communications to your health insurer to get approval for the treatment that we recommend. For example, if a hospital admission is recommended, we may need to disclose information to your health insurer to get prior approval for the hospitalization. We may also disclose protected health information to your insurance company to determine whether you are eligible for benefits or whether a particular service is covered under your health plan. In order to get payment for your services, we may also need to disclose your protected health information to your insurance company to demonstrate the medical necessity of the services, or as required by your insurance company, for utilization review. We may also disclose patient information to another provider involved in your care for the other provider's payment activities. We may release information to an outside agency for collection purposes.

C. Operations. We may use or disclose your protected health information, as necessary, for our own health care operations in order to facilitate the function of NSU and to provide quality care to all patients. Health care operations include such activities as

- Quality assessment and improvement activities
- Employee review activities
- Training programs including those in which students, trainees, or practitioners in health care learn under supervision
- Accreditation, certification, licensing, or credentialing activities
- Review and auditing, including compliance reviews, medical reviews, legal services, and maintaining compliance programs
- Business management and general administrative activities

In certain situations, we may also disclose patient information to another provider or health plan for their health care operations.

D. Other Uses and Disclosures. As part of treatment, payment, and health care operations, we may also use or disclose your protected health information for the following purposes:

- To remind you of an appointment (Appointment reminders may be communicated by mail or by leaving a message on the answering machine of a telephone number that you have provided.)

- To inform you of potential treatment alternatives or options
- To inform you of health-related benefits or services that may be of interest to you

II. Uses and Disclosures Beyond Treatment, Payment, and Health Care Operations Permitted Without Authorization or Opportunity to Object

Federal privacy rules allow us to use or disclose your protected health information without your permission or authorization for a number of reasons including the following:

A. When Legally Required. We will disclose your protected health information when we are required to do so by any Federal, State or local law.

B. When There Are Risks to Public Health. We may disclose your protected health information for the following public activities and purposes:

- To prevent, control, or report disease, injury, or disability as permitted by law
- To report vital events such as birth or death as permitted or required by law
- To conduct public health surveillance, investigations, and interventions as permitted or required by law
- To collect or report adverse events and product defects; track FDA-regulated products; and enable product recalls, repairs, or replacements to the FDA and conduct post-marketing surveillance
- To notify a person who has been exposed to a communicable disease or who may be at risk of contracting or spreading a disease as authorized by law
- To report to an employer information about an individual who is a member of the workforce as legally permitted or required

C. To Report Abuse, Neglect, or Domestic Violence. We may notify government authorities if we believe that a patient is the victim of abuse, neglect, or domestic violence. It is the responsibility of any/all personnel to alert the proper authorities in the event a minor, elderly, or vulnerable adult patient is identified as a victim of alleged or suspected neglect or abuse including sexual abuse, and to comply with proper procedures for the reporting as required or authorized by law.

D. To Conduct Health Oversight Activities. We may disclose your protected health information to a health oversight agency for activities including audits; civil, administrative, or criminal investigations, proceedings, or actions; inspections; licensure or disciplinary actions; or other activities necessary for appropriate oversight as authorized by law. We will not disclose your health information if you are the subject of an investigation and your health information is not directly related to your receipt of health care or public benefits.

E. In Connection with Judicial and Administrative Proceedings. We may disclose your protected health information in the course of any judicial or administrative proceeding in response to an order of a court or administrative tribunal as expressly authorized by such order or in response to a subpoena if you have been notified of the request for information.

F. For Law Enforcement Purposes. We may disclose your protected health information to a law enforcement official for law enforcement purposes as follows:

- As required by law for reporting of a gunshot wound or life-threatening injury indicating an act of violence
- Pursuant to court order, court-ordered warrant, subpoena, summons or similar process
- For the purpose of identifying or locating a suspect, fugitive, material witness, or missing person
- Under certain limited circumstances, when you are the victim of a crime
- To a law enforcement official if NSU has a suspicion that your death was the result of criminal conduct
- In an emergency in order to report a crime
- In the event a minor, elderly, or vulnerable adult patient is identified as a victim of alleged or suspected neglect or abuse including sexual abuse

G. To Coroners, Funeral Directors, and for Organ Donation. We may disclose protected health information to a coroner or medical examiner for identification purposes, to determine cause of death, or for the coroner or medical examiner to perform other duties authorized by law. We may also disclose protected health information to a funeral director, as authorized by law, in order to permit the funeral director to carry out his or her duties. We may disclose such information in reasonable anticipation of death. Protected health information may be used and disclosed for cadaveric organ, eye, or tissue donation purposes.

H. For Research Purposes. We may use or disclose your protected health information for research without your authorization in limited circumstances only if the use or disclosure for research has been approved by an institutional review board or privacy board that has reviewed the research proposal and research protocols and decided that your

information is necessary to the research and the privacy of your information will be protected.

I. In the Event of a Serious Threat to Health or Safety. We may, consistent with applicable law and ethical standards of conduct, use or disclose your protected health information if we believe, in good faith, that such use or disclosure is necessary to prevent or lessen a serious and imminent threat to your health or safety or to the health and safety of the public.

J. For Specified Government Functions. In certain circumstances, the Federal regulations authorize NSU to use or disclose your protected health information to facilitate specified government functions relating to military and veterans activities, national security and intelligence activities, protective services for the President and others, medical suitability determinations, correctional institutions, and law enforcement custodial situations.

K. For Worker's Compensation. We may release your health information to comply with worker's compensation laws or similar programs.

III. Uses and Disclosures Permitted Without Authorization, but with Opportunity to Object

We may disclose your protected health information to your family member(s) or a close personal friend if it is directly relevant to the person's involvement in your care or payment related to your care. We can also disclose your information in connection with trying to locate or notify family member(s) or others involved in your care concerning your location, condition, or death.

You may object to these disclosures. If you do not object to these disclosures or we can infer from the circumstances that you do not object or we determine, in the exercise of our professional judgment, that it is in your best interests for us to make disclosure of information that is directly relevant to the person's involvement with your care, we may disclose your protected health information as described.

IV. Uses and Disclosures Which You Authorize

Other than as stated above, we will not disclose your health information other than with your written authorization. You may revoke your authorization in writing at any time except to the extent that we have taken action in reliance upon the authorization.

V. Your Rights

You have the following rights regarding your health information:

A. The Right to Inspect and Copy Your Protected Health Information. You may inspect and obtain a copy of your protected health information that is contained in a designated record set for as long as we maintain the protected health information. A "designated record set" contains medical and billing records and any other records that are used to make decisions about you.

Under Federal law, however, you may not inspect or copy the following records: psychotherapy notes; information compiled in reasonable anticipation of, or for use in, a civil, criminal, or administrative action or proceeding; and protected health information that is subject to a law that prohibits access to protected health information. Depending on the circumstances, you may have the right to have a decision to deny access reviewed.

We may deny your request to inspect or copy your protected health information if, in our professional judgment, we determine that the access requested is likely to endanger your life or safety or that of another person, or that it is likely to cause substantial harm to another person referenced within the information. You have the right to request a review of this decision.

To inspect or copy your medical information, you must submit a written request to the NSU Health Care Center/Clinic where you received services and direct the correspondence to the Privacy Contact. The contact information for that NSU Health Care Center/Clinic is attached to this Notice. If you request a copy of your information, we may charge you a fee for the costs of copying, mailing, or other costs incurred by us in complying with your request.

Please contact our Privacy Officer if you have questions about access to your medical record.

B. The Right to Request a Restriction on Uses and Disclosures of Your Protected Health Information. You may ask us, in writing, not to use or disclose certain parts of your protected health information for the purposes of treatment, payment, or health care operations. You may also request, in writing, that we not disclose your health information to family members or friends who may be involved in your care or for notification purposes as described in this Notice of Privacy Practices. Your request must state the specific restriction requested and to whom you want the restriction to apply.

NSU is not required to agree to a restriction that you may request. We will notify you in writing if we deny your request

to a restriction. If NSU does agree to the requested restriction, we may not use or disclose your protected health information in violation of that restriction unless it is needed to provide emergency treatment. Under certain circumstances, we may terminate our agreement to a restriction. You may request, in writing, a restriction by contacting the Privacy Contact at the NSU Health Care Center/Clinic where you received services.

C. The Right to Request to Receive Confidential Communications from Us by Alternative Means or at an Alternative Location. You have the right to request that we communicate with you in certain ways. We will accommodate reasonable requests. We may condition this accommodation by asking you for information as to how payment will be handled or specification of an alternative address or other method of contact. We will not require you to provide an explanation for your request. Requests must be made, in writing, to the Privacy Contact at the NSU Health Care Center/Clinic where you received services.

D. The Right to Request Amendment of Your Protected Health Information. You may request an amendment of protected health information about you in a designated record set for as long as we maintain this information. If you believe that there is a mistake or missing information in our record of your protected health information, you may request, in writing, that we correct or add to the record. In this written request, you must also provide a reason to support the requested amendment. We will respond within 60 days of receiving your request. We may deny the request if we determine that the protected health information is: (1) correct and complete; (2) not created by us and/or not part of our records, or; (3) not permitted to be disclosed. Any denial will state the reasons for denial and explain your rights to have the request and denial, along with any statement in response that you provide, appended to your protected health information. If we approve the request for amendment, we will change the protected health information and so inform you. Requests for amendment must be directed to the Privacy Contact at the NSU Health Care Center/Clinic where you received services.

E. The Right to Receive an Accounting. You have the right to request, in writing, an accounting of certain disclosures of your protected health information made by NSU. This right applies to disclosures for purposes other than treatment, payment, or health care operations as described in this Notice of Privacy Practices. We are also not required to account for disclosures that you requested, disclosures that you agreed to by signing an authorization form, disclosures for a facility directory, disclosures to friends or family members involved in your care, or certain other disclosures we are permitted to make without your authorization. The request for an accounting must be made, in writing, to the Privacy Contact at the NSU Health Care Center/Clinic where you received services. The request should specify the time period sought for the accounting. We are not required to provide an accounting for disclosures that take place prior to April 14, 2003. Accounting requests may not be made for periods of time in excess of six years. We will provide the first accounting you request during any 12-month period without charge. Subsequent accounting requests may be subject to a reasonable cost-based fee.

F. The Right to Obtain a Paper Copy of This Notice. Upon request, we will provide a separate paper copy of this notice even if you have already received a copy of the notice or have agreed to accept this notice electronically.

VI. Our Duties

NSU is required by law to maintain the privacy of your health information and to provide you with this Notice of our duties and privacy practices. We are required to abide by terms of this Notice as may be amended from time to time. We reserve the right to change the terms of this Notice and to make the new Notice provisions effective for all protected health information that we maintain. If NSU changes its Notice, we will provide a copy of the revised Notice on your next office visit to the NSU Health Care Center/Clinic.

VII. Complaints

You have the right to express complaints to NSU and to the Secretary of Health and Human Services if you believe that your privacy rights have been violated. You may complain to NSU by contacting, in writing, to the Privacy Contact at the NSU Health Care Center/Clinic where you received services. We encourage you to express any concerns you may have regarding the privacy of your information. You will not be retaliated against in any way for filing a complaint.

VIII. Effective Date

This Notice is effective April 14, 2003.

NSU NOVA SOUTHEASTERN UNIVERSITY

Acknowledgement of Receipt of HIPAA Notice of Privacy Practices

I acknowledge that I have received the attached HIPAA Notice of Privacy Practices.

Signature of patient or representative	Printed name	Date

If Personal Representative's signature appears above, please describe Personal Representative's relationship to the patient.

_____

_____

Appendix C

Demographic Information

Participant #:_____

Please enter the following information on this form:

1. Age (years):_____

2. Age (years) when diagnosed:_____

3. Type of Primary Immunodeficiency (diagnosis):

4. Type of physician in charge of managing your primary immunodeficiency (for example, Immunologist):

5. Current treatment for PI:

a. IVIG: Brand_____

Dose (grams)_____

Frequency (how often)_____

b. SCIG: Brand_____

Dose (grams)_____

Frequency (how often)_____

c. Prophylactic Antibiotics:

Brand_____

Dose_____

Frequency_____

d. Other medications **relating** to PI (for example, steroids). Do not include non-PI related medications.

Choose one answer for each of the following questions:

6. Gender

Male

Female

7. Ethnicity

White
Hispanic or Latino
Black or African American
Native American or American Indian
Native Hawaiian or Pacific Islander
Asian
Other

8. Employment Status

Full-time
Part-time
Temporary
Pool/Per Diem
Unemployed
Military
Disabled
Retired
Student
Other

9. Type of health insurance

Preferred Provider Organization (PPO)
Health Maintenance Organization (HMO)
Exclusive Provider Organization (EPO)
Point of Service Plan (POS)
High Deductible Health Plan (HDHP)
Short Term Health Insurance Plan
Medicare
Medicaid
Veteran Benefits/Tricare
Other

10. Total household income prior to taxes in the past year?

Less than $25,000

$25,000-34,999

$35,000-49,999

$50,000-74,999

$75,000-99,999

$100,000-149,999

More than $150,000

Appendix D

Infection Report

Participant #_____

The following questions will ask you to recall information about your health **during the 8 weeks** you have participated in the study. Please answer the questions, keeping only the **past 8 weeks, during the study period** in mind.

1. Number of infections/illnesses that did **NOT** require medical attention or new/additional medication(s):_____

2. Number of infections/illnesses that did require medical attention or new/additional medication(s):_____

3. Number of non-planned medical appointments related specifically to your primary immunodeficiency:

   a. Urgent care visits:_____

   b. Emergency room visits:_____

   c. Sick visits to a primary care physician:_____

   d. Sick visits to physician in charge of your PI diagnosis:_____

   e. Other (describe):_____

   _____

Appendix E

Pre/Post-study Surveys (Outcome Measures)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very Good	Good	Fair	Poor
1	2	3	4	5

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
1	2	3	4	5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing <u>several</u> flights of stairs	1	2	3
e. Climbing <u>one</u> flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking <u>more than a mile</u>	1	2	3
h. Walking <u>several hundred yards</u>	1	2	3
i. Walking <u>one hundred yards</u>	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Were limited in the kind of work of other activities	1	2	3	4	5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	1	2	3	4	5
b. Accomplished less than you would like	1	2	3	4	5
c. Did work or other activities less carefully than usual	1	2	3	4	5

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
1	2	3	4	5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
1	2	3	4	5	6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
1	2	3	4	5

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you feel full of life?	1	2	3	4	5
b. Have you been very nervous?	1	2	3	4	5
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5
d. Have you felt calm and peaceful?	1	2	3	4	5
e. Did you have a lot of energy?	1	2	3	4	5
f. Have you felt downhearted and depressed?	1	2	3	4	5
g. Did you feel worn out?	1	2	3	4	5
h. Have you been happy?	1	2	3	4	5
i. Did you feel tired?	1	2	3	4	5

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little bit of the time	None of the time
1	2	3	4	5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Thank you for completing these questions!

Fatigue Impact Scale

Patient Number: _____ _____

Below is a list of statements that describe how fatigue may cause problems in people's lives. Please read each statement carefully. Circle the number that indicates best how much of a problem fatigue has been for you these **past four (4) weeks**, including today. Please circle one number for each statement and do not skip any statements.

Circle one number on each line	No Problem	Small Problem	Moderate Problem	Big Problem	Extreme Problem
1. *Because of my fatigue…* **I feel less alert.**	0	1	2	3	4
2. *Because of my fatigue…* **I feel that I am more isolated from social contact.**	0	1	2	3	4
3. *Because of my fatigue…* **I have to reduce my workload or responsibilities.**	0	1	2	3	4
4. *Because of my fatigue…* **I am more moody.**	0	1	2	3	4
5. *Because of my fatigue…* **I have difficulty paying attention for a long period of time.**	0	1	2	3	4
6. *Because of my fatigue…* **I feel like I cannot think clearly.**	0	1	2	3	4
7. *Because of my fatigue…* **I work less effectively. (This applies to work inside or outside the home).**	0	1	2	3	4
8. *Because of my fatigue…* **I have to rely more on others to help me or do things for me.**	0	1	2	3	4
9. *Because of my fatigue…* **I have difficulty planning activities ahead of time because my fatigue may interfere with them.**	0	1	2	3	4
10. *Because of my fatigue…* **I am more clumsy and uncoordinated.**	0	1	2	3	4
11. *Because of my fatigue…* **I find that I am more forgetful.**	0	1	2	3	4
12. *Because of my fatigue…* **I am more irritable and more easily angered.**	0	1	2	3	4
13. *Because of my fatigue…* **I have to be careful about pacing my physical activities.**	0	1	2	3	4
14. *Because of my fatigue…* **I am less motivated to do anything that requires physical effort.**	0	1	2	3	4
15. *Because of my fatigue…* **I am less motivated to engage in social activities.**	0	1	2	3	4
16. *Because of my fatigue…* **My ability to travel outside my home is limited.**	0	1	2	3	4
17. *Because of my fatigue…* **I have trouble maintaining physical effort for long periods.**	0	1	2	3	4
18. *Because of my fatigue…* **I find it difficult to make decisions.**	0	1	2	3	4
19. *Because of my fatigue…* **I have few social contacts outside of my own home.**	0	1	2	3	4
20. *Because of my fatigue…* **Normal day-to-day events are stressful for me.**	0	1	2	3	4

Circle one number on each line	No Problem	Small Problem	Moderate Problem	Big Problem	Extreme Problem
21. *Because of my fatigue…* **I am less motivated to do anything that requires thinking.**	0	1	2	3	4
22. *Because of my fatigue…* **I avoid situations that are stressful for me.**	0	1	2	3	4
23. *Because of my fatigue…* **My muscles feel much weaker than they should.**	0	1	2	3	4
24. *Because of my fatigue…* **My physical discomfort is increased.**	0	1	2	3	4
25. *Because of my fatigue…* **I have difficulty dealing with anything new.**	0	1	2	3	4
26. *Because of my fatigue…* **I am less able to finish tasks that require thinking.**	0	1	2	3	4
27. *Because of my fatigue…* **I feel unable to meet the demands that people place on me.**	0	1	2	3	4
28. *Because of my fatigue…* **I feel less able to provide financial support for myself and my family.**	0	1	2	3	4
29. *Because of my fatigue…* **I engage in less sexual activity.**	0	1	2	3	4
30. *Because of my fatigue…* **I find it difficult to organize my thoughts when I am doing things at home or at work.**	0	1	2	3	4
31. *Because of my fatigue…* **I am less able to complete tasks that require physical effort.**	0	1	2	3	4
32. *Because of my fatigue…* **I worry about how I look to other people.**	0	1	2	3	4
33. *Because of my fatigue…* **I am less able to deal with emotional issues.**	0	1	2	3	4
34. *Because of my fatigue…* **I feel slowed down in my thinking.**	0	1	2	3	4
35. *Because of my fatigue…* **I find it hard to concentrate.**	0	1	2	3	4
36. *Because of my fatigue…* **I have difficulty participating fully in family activities.**	0	1	2	3	4
37. *Because of my fatigue…* **I have to limit my physical activities.**	0	1	2	3	4
38. *Because of my fatigue…* **I require more frequent or longer periods of rest.**	0	1	2	3	4
39. *Because of my fatigue…* **I am not able to provide as much emotional support to my family as I should.**	0	1	2	3	4
40. *Because of my fatigue…* **Minor difficulties seem like major difficulties.**	0	1	2	3	4

PERCEIVED STRESS SCALE

The questions in this scale ask you about your feelings and thoughts during the last month. **In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.**

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

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The PSS Scale is reprinted with permission of the American Sociological Association, from Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*, 386-396.

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EXERCISE BENEFITS/BARRIERS SCALE

DIRECTIONS: Below are statements that relate to ideas about exercise. Please indicate the degree to which you agree or disagree with the statements by circling SA for strongly agree, A for agree, D for disagree, or SD for strongly disagree.

		Strongly Agree	Agree	Disagree	Strongly Disagree
1.	I enjoy exercise.	SA	A	D	SD
2.	Exercise decreases feelings of stress and tension for me.	SA	A	D	SD
3.	Exercise improves my mental health.	SA	A	D	SD
4.	Exercising takes too much of my time.	SA	A	D	SD
5.	I will prevent heart attacks by exercising.	SA	A	D	SD
6.	Exercise tires me.	SA	A	D	SD
7.	Exercise increases my muscle strength.	SA	A	D	SD
8.	Exercise gives me a sense of personal accomplishment.	SA	A	D	SD
9.	Places for me to exercise are too far away.	SA	A	D	SD
10.	Exercising makes me feel relaxed.	SA	A	D	SD
11.	Exercising lets me have contact with friends and persons I enjoy.	SA	A	D	SD
12.	I am too embarrassed to exercise.	SA	A	D	SD
13.	Exercising will keep me from having high blood pressure.	SA	A	D	SD
14.	It costs too much to exercise.	SA	A	D	SD
15.	Exercising increases my level of physical fitness.	SA	A	D	SD
16.	Exercise facilities do not have convenient schedules for me.	SA	A	D	SD
17.	My muscle tone is improved with exercise.	SA	A	D	SD
18.	Exercising improves functioning of my cardiovascular system.	SA	A	D	SD
19.	I am fatigued by exercise.	SA	A	D	SD
20.	I have improved feelings of well being from exercise.	SA	A	D	SD
21.	My spouse (or significant other) does not encourage exercising.	SA	A	D	SD

(Continued on reverse side)

		Strongly Agree	Agree	Disagree	Strongly Disagree
22.	Exercise increases my stamina.	SA	A	D	SD
23.	Exercise improves my flexibility.	SA	A	D	SD
24.	Exercise takes too much time from family relationships.	SA	A	D	SD
25.	My disposition is improved with exercise.	SA	A	D	SD
26.	Exercising helps me sleep better at night.	SA	A	D	SD
27.	I will live longer if I exercise.	SA	A	D	SD
28.	I think people in exercise clothes look funny.	SA	A	D	SD
29.	Exercise helps me decrease fatigue.	SA	A	D	SD
30.	Exercising is a good way for me to meet new people.	SA	A	D	SD
31.	My physical endurance is improved by exercising.	SA	A	D	SD
32.	Exercising improves my self-concept.	SA	A	D	SD
33.	My family members do not encourage me to exercise.	SA	A	D	SD
34.	Exercising increases my mental alertness.	SA	A	D	SD
35.	Exercise allows me to carry out normal activities without becoming tired.	SA	A	D	SD
36.	Exercise improves the quality of my work.	SA	A	D	SD
37.	Exercise takes too much time from my family responsibilities.	SA	A	D	SD
38.	Exercise is good entertainment for me.	SA	A	D	SD
39.	Exercising increases my acceptance by others.	SA	A	D	SD
40.	Exercise is hard work for me.	SA	A	D	SD
41.	Exercise improves overall body functioning for me.	SA	A	D	SD
42.	There are too few places for me to exercise.	SA	A	D	SD
43.	Exercise improves the way my body looks.	SA	A	D	SD

Self-efficacy For Exercise (SEE) Scale

How confident are you right now that you could exercise three times per week for 20 minutes if:

	Not Confident										Very Confident
1. The weather was bothering you	0	1	2	3	4	5	6	7	8	9	10
2. You were bored by the program or activity	0	1	2	3	4	5	6	7	8	9	10
3. You felt pain when exercising	0	1	2	3	4	5	6	7	8	9	10
4. You had to exercise alone	0	1	2	3	4	5	6	7	8	9	10
5. You did not enjoy it	0	1	2	3	4	5	6	7	8	9	10
6. You were too busy with other activities	0	1	2	3	4	5	6	7	8	9	10
7. You felt tired	0	1	2	3	4	5	6	7	8	9	10
8. You felt stressed	0	1	2	3	4	5	6	7	8	9	10
9. You felt depressed	0	1	2	3	4	5	6	7	8	9	10

Subjective Exercise Experience Scale

How Do You Feel?

This inventory contains a number of items designed to reflect how you feel at this particular moment in time (i.e., Right Now). Please circle the number on each item that indicates **HOW YOU FEEL RIGHT NOW.**

I FEEL:

1. Great						
1	2	3	4	5	6	7
not at all			moderately			very much so
2. Awful						
1	2	3	4	5	6	7
not at all			moderately			very much so
3. Drained						
1	2	3	4	5	6	7
not at all			moderately			very much so
4. Positive						
1	2	3	4	5	6	7
not at all			moderately			very much so
5. Crummy						
1	2	3	4	5	6	7
not at all			moderately			very much so
6. Exhausted						
1	2	3	4	5	6	7
not at all			moderately			very much so
7. Strong						
1	2	3	4	5	6	7
not at all			moderately			very much so
8. Discouraged						
1	2	3	4	5	6	7
not at all			moderately			very much so
9. Fatigued						
1	2	3	4	5	6	7
not at all			moderately			very much so
10. Terrific						
1	2	3	4	5	6	7
not at all			moderately			very much so

11. Miserable

1	2	3	4	5	6	7
not at all			moderately			very much so

12. Tired

1	2	3	4	5	6	7
not at all			moderately			very much so

****

Subjective Exercise Experiences Scale :

PWB = 1 + 4 + 7 + 10
PD = 2 + 5 + 8 + 11
FAT = 3 + 6 + 9 + 12

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Appendix F

Interview Questions (All Participants)

- Tell me about your current quality of life.
- How do you think stress impacts your life?
- What things help reduce your stress?
- Tell me how fatigue impacts your life.
- What things help improve your fatigue?
- Tell me about cognitive changes you have experienced.
- How does your diagnosis of a primary immunodeficiency impact your quality of life, fatigue, or stress?

Questions (Specific to Exercise Group)

- Tell me about your experience participating in the exercise program during the past eight weeks?
- How do you think exercise affects your quality of life?
- How do you think exercise impacts your primary immunodeficiency?

Questions (Specific to Control Group)

- Tell me about your past experiences with exercise.
- How do you think exercise could impact your diagnosis of primary immunodeficiency or your quality of life?

Appendix G

Sample Exercise Program

Physitrack **General core program 2** Page 1 of 3

1 rep, 2 sets, 20 min duration, 80 thr, 1 rpe

1. Biking

Consult with your therapist how long you can cycle and at what interval you can continue.

1 rep, 2 sets, 30 min duration, 80 thr

2. Walking

Consult with your therapist how long you can walk and at what interval you can continue.

10 reps, 3 sets

3. Pilates pelvic curl

Lie on your back in a neutral spine position. Bend your legs, keeping your knees and feet parallel and at hip width apart with your arms by your sides. INHALE: no movement EXHALE: draw the abdominals in and roll up, lifting your pelvis off the mat INHALE: no movement EXHALE: roll your spine down onto the mat Roll your back up and down, articulating your spine vertebrae by vertebrae. Maintain your knees parallel and do not allow them to open.

10 reps, 3 sets

4. Pilates single leg lift

Lie on your back in a neutral spine position. Bend your legs, keeping your knees and feet parallel and at hip width apart with your arms by your sides. EXHALE: lift your leg off the mat with the bent knee at a 90 degree angle and your foot Plantar flexed (pointed). INHALE: lower your leg down and tap the floor with your toe. Perform the desired number of the repetitions and change legs. Keep the pelvis stable as you raise and lower your leg, hinging at the hip joint. Maintain your leg bent at a constant angle of 90 degrees.

10 reps, 3 sets

5. Pilates side leg lift

Lie on your side with your head resting on your bottom arm which should be stretched straight outwards. Place your top arm on the mat with the elbow bent in front of you for balance. Your pelvis should be perpendicular to the mat with your legs pressing together and slightly to the front. EXHALE: lift both legs off the mat, keeping them locked. INHALE: lower your legs back down but do not touch the mat Keep your feet aligned and together and up off the mat throughout the exercise and use your abdominals to raise your legs upwards.

Physitrack

General core program 2

10 reps, 2 sets, 5 s hold

6. Curl ups

Lie on your back with your knees bent and your arms crossed over your chest with your lumbar spine pressed towards the floor. Breathe in, and then exhale as you lift your shoulders off the floor. Keep your abdominal muscles tight as your curl up off the floor and do not allow your lumbar spine to raise off the mat. Return back down to the starting position in slow controlled manner and repeat.

10 reps, 2 sets, 5 s hold

7. Sit-backs

Sit on the floor with your knees bent and your arms folded across your chest. Slowly sit back as far as comfortable while maintaining a flat back, then return to the starting position. Make sure your feet stay in contact with the floor.

10 reps, 3 sets

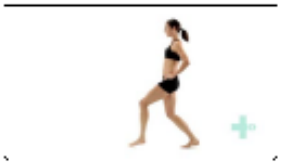
8. "X" Jump drill

Make an X-pattern. Jump forward, bringing your feet together, then jump forward bringing your feet out. Reverse this movement by jumping back, bringing your feet together, and them jump back bringing your feet out.

10 reps, 2 sets

9. Bird dog

Start on your hands and knees, with your hands under your shoulders, and knees under your hips. Tighten the abdominal core muscles. Extend the opposite leg and the opposite arm simultaneously, making sure your maintain good control in your torso. Do not allow your body or hips to rotate. Repeat on the other side.



10 reps, 2 sets

10. Lunges - bodyweight

Stand straight with your arms to the side or on your hips. Take a large step forwards on your affected leg, then drop your hips directly down between both feet, bending your hips and knees to a 90 degrees. Push back up to the starting position, and repeat. Make sure you take a large enough step that your front knee does not travel over your foot, and ensure your knee travels directly forwards. Keep your body up straight throughout the movement.

Physitrack

General core program 2

11. Core activation - single leg, arms to leg flexion

Lie on your back with one knee bent and one leg straightened. Bring your arms up over your head and breathe in. As you breath out, bend your straight leg in towards your chest whilst lifting your head and hugging it with your arms. Straighten the leg and the arms back down as you breath in, and then repeat the movement.

10 reps, 2 sets

12. Biceps curls - seated with dumbbells

Sit on a bench holding a set of dumbbells in each hand. Flex your arms simultaneously and bring the weights up towards your shoulders, curling from your elbows. Lower the dumbbells back down until your elbows are fully extended. Ensure the movement remains within your arms and you are not using your hips or shoulders.

10 reps, 2 sets, 2lbs weight

13. Chest press with weights

Lie on your back with your legs bent, feet on the floor and a weight in each hand. Bring your arms out to the side and bend your elbows. Reach the weights directly up to the ceiling, and control the movement back down to the start position with your elbows out to the side.

10 reps, 2 sets, 2lbs weight

14. Jogging high knees

Jog on the spot bringing your knees up as high as you can. Make sure you land lightly on the balls of your feet, springing the leg quickly back up.

1 rep, 5 sets, 1 min duration

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